Apathy and Effort-Based Decision Making: A Cognitive Mechanism Underlying Amotivated Behaviour

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Apathy is a common, debilitating but poorly understood disorder of motivation that manifests in reduced goal directed behaviours. The integration of cost and reward information about potential actions is central to normal motivated behaviour. This thesis will argue that disruption of this normal process – often termed effort-based decision making – underlies the clinical syndrome of apathy.

Two broad sets of questions are investigated to address this hypothesis, in clinically apathetic patients with either Parkinson's disease (PD) or a genetic form of cerebral small vessel disease (SVD). Firstly, are apathetic patients hypersensitive to effort costs, or insensitive to rewards when making decisions about potential actions? Do these changes associated with apathy map onto physiological alterations in reward processing and disruption of anatomical regions that underlie normal effort-based decision making? And do these behavioural changes occur along the same axis as those induced by dopamine depletion? Secondly, using an ecological framework of decision making in which participants must compare current (foreground) reward information to the background reward context to guide adaptive behaviour, this research explores whether apathy is associated with aberrant use of background reward information, and how this interacts with the dopaminergic system.

The studies demonstrate effort-based decision making is disrupted in patients with apathy, driven by reduced incentivisation by the rewarding outcomes of actions rather than hypersensitivity to effort costs themselves. Reward insensitivity manifests in both behavioural choices and physiological responses to incentives, is associated with reduced white matter integrity in tracts connecting regions crucial for effort-based decision making, but occurs along a separate mechanistic axis to changes induced by dopamine depletion. Furthermore, whilst healthy human decision makers are remarkably sensitive to changes in background reward environment, apathy changed the influence of this information – dependent on dopaminergic tone. Together, the work in this thesis presents evidence that disruption of a specific cognitive process underlies the apathetic syndrome. This advances understanding of normal motivated behaviour and identifies potential therapeutic avenues to treat this important clinical syndrome.

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1 GENERAL INTRODUCTION

1.1 Apathy – general considerations

Apathy is a syndrome of loss of motivation and concomitant reduced goal directed behaviours that occurs in a broad range of neurological and psychiatric conditions. Apathetic patients report that they "*can't be bothered*", that activities "*don't seem worth it*", or often that they "*just don't know*" why they no longer engage in behaviours they used to do. But despite its high prevalence and clear impact on quality of life for both patients and their families, a mechanistic understanding of this condition remains elusive. A striking feature of the apathy phenotype is how similar it is across a disparate range of underlying pathologies. This suggests a common systems-level disruption might underlie the apathetic syndrome, and the overarching aim of this thesis is to test this hypothesis. Specifically, I investigate whether effort-based decision making – the process of deciding whether an action, or series of actions, is worth it based on a comparison between the action costs and the potential rewarding outcomes – is disrupted in patients with apathy. To achieve this broad aim, I use a combination of novel behavioural decision making paradigms, autonomic recordings, neuroimaging techniques and drug manipulations, designed to assess effort-based decision making and its component processes in two separate clinical populations – genetic cerebral small vessel disease (CADASIL) and Parkinson's disease, as well as healthy controls. As outlined in the following chapters, the results suggest that the processes underlying effort-based decision making are disrupted in apathetic patients, providing a mechanistic explanation for the reduced goal directed behaviour that defines this debilitating condition.

1.1.1 Definition

A common definition of apathy, across conditions and healthcare settings, is crucial for enabling effective study and treatment of the syndrome. This has been addressed within specific diseases, particularly Alzheimer's disease (Robert et al., 2009) and Parkinson's disease (Dujardin et al., 2007), as well as more generally (Levy and Dubois, 2006;

Marin, 1991). With the exception of Levy and Dubois, these authors emphasise *loss of motivation* as the central feature of apathy, a loss which is inferred from observations of an individual's behaviour and affect. Furthermore, these definitions conceptualise reduced motivation occurring within three core domains:

- **Behavioural** (reduced self-initiated behaviour and responses to environmental triggers)
- **Cognitive** (reduced curiosity and ideas, either spontaneous or in response to environmental factors)
- **Emotional** (reduced responses to positive and negative environmental stimuli)

To fulfil criteria for apathy, Robert et al proposed impairment in at least two of these domains resulting in functional impairment, as well as the absence of secondary causes (Robert et al., 2009, **Figure 1)**.

Apathy proposed criteria

For a diagnosis of Apathy the patient should fulfil the criteria A, B, C and D

A Loss of or diminished motivation in comparison to the patient's previous level of functioning and which is not consistent with his age or culture. These changes in motivation may be reported by the patient himself or by the observations of others.

B Presence of at least one symptom in at least two of the three following domains for a period of at least four weeks and present most of the time

Domain B1 : Loss of, or diminished, goal-directed behaviour as evidenced by at least one of the following:

- Loss of self-initiated behaviour (for example: starting conversation, doing basic tasks of day-to-day living, seeking social activities, communicating choices)
- Loss of environment-stimulated behaviour (for example: responding to conversation, participating in social activities)

Domain B2 : Loss of, or diminished, goal-directed cognitive activity as evidenced by at least one of the following:

- Loss of spontaneous ideas and curiosity for routine and new events (i.e., challenging tasks, recent news, social opportunities, personal/family and social affairs).
- Loss of environment-stimulated ideas and curiosity for routine and new events (i.e., in the persons residence, neighbourhood or community)

Domain B3 : Loss of, or diminished, emotion as evidenced by at least one of the following:

- Loss of spontaneous emotion, observed or self-reported (for example, subjective feeling of weak or absent emotions, or observation by others of a blunted affect)
- Loss of emotional responsiveness to positive or negative stimuli or events (for example, observer-reports of unchanging affect, or of little emotional reaction to exciting events, personal loss, serious illness, emotional-laden news)

C These symptoms (A–B) cause clinically significant impairment in personal, social, occupational, or other important areas of functioning.

D The symptoms (A–B) are not exclusively explained or due to physical disabilities (e.g. blindness and loss of hearing), to motor disabilities, to diminished level of consciousness or to the direct physiological effects of a substance (e.g. drug of abuse, a medication).

Figure 1-1. Proposed diagnostic criteria for apathy in Alzheimer's disease

From (Robert et al., 2009)

An alternative approach to defining apathy was proposed by Levy and Dubois, building on the earlier work of Marin (Levy and Dubois, 2006; Marin, 1991). Marin defined motivation as *the characteristics and determinants of goal-directed behaviour,* whilst Levy and Dubois suggested dispensing with the term motivation altogether, considering it a *blurred and inhomogeneous psychological concept*. Instead, they suggested apathy

was *the quantitative reduction of self-generated voluntary and purposeful behaviour*. This shift, whilst still retaining the same broad schematic (including the three proposed sub-domains of apathy, albeit with subtle changes), emphasised the concept of apathy as a disorder of goal directed behaviour, pointing more directly at potential cognitive systems that may underlie the syndrome (Levy and Dubois, 2006).

Currently, apathy is often referred to in the literature as a disorder of motivation, a disorder of motivated behaviour or a disorder of goal directed behaviour, but is generally defined on the basis of questionnaire assessments. This creates a degree of heterogeneity in apathy populations across studies, although by and large the different questionnaire measures overlap to a considerable degree (Radakovic et al., 2015). Historically terms such as abulia and auto-activation deficit have also been used to describe clinical syndromes which broadly overlap with current definitions of apathy.

In this thesis I primarily use the Lille Apathy Rating Scale (LARS) to define apathy, with a cut-off score of > -22 (Sockeel et al., 2006) – see **Questionnaire methods to assess apathy** and **Appendix 1**. Because I aim to investigate the mechanisms underlying apathy based on current neuroscientific understanding of normal motivated behaviour, for the most part I treat apathy as a generalised construct – a disorder of goal directed behaviour – rather than focusing on the proposed subdomains discussed above. Although they may be potentially relevant to a mechanistic understanding of the apathetic syndrome, at this stage it remains unclear how these questionnaire-derived components may map onto dissociable neurobiological systems (Le Heron et al., 2017).

1.1.2 Epidemiology

A number of neurodegenerative, vascular, inflammatory, infectious and traumatic brain pathologies have been associated with the development of apathy Table 1-1, in addition to its association with certain psychiatric conditions including schizophrenia and depression (Foussias et al., 2014; Kos et al., 2016; Le Heron et al., 2017; Treadway and Zald, 2011). In this thesis, I focus on two clinical groups – cerebral small vessel disease and Parkinson's disease – in whom apathy occurs commonly, often with significant

deleterious consequences. However, the results presented here may potentially be extrapolated to apathy occurring in other disorders.

Table 1-1. Neurological conditions associated with apathy

Condition	Prevalence	Comments
Sporadic SVD	15-30%	An increasingly recognised complication of SVD, with a clear association between apathy and both background vascular risk factors and imaging changes of SVD (Hollocks et al., 2015; Ligthart et al., 2012; van der Mast et al., 2008)
CADASIL	40%	One of the cardinal features of this condition. Occurs at all clinical stages but more likely with progression of disease (Reyes et al., 2009).
Stroke (large vessel territory)	~30%	Occurrence is associated with worse outcomes and poorer quality of life (Caeiro et al., 2013; Mayo et al., 2009).
Parkinson's disease	17-70% (likely ~30% in general population)	A common non-motor symptom of PD. Occurs at all stages of disease, and is a presenting symptom in >20% of patients. Clear evidence it is an intrinsic (rather than reactive) feature of PD (Aarsland et al., 2009; Dujardin et al., 2007; Pagonabarraga et al., 2015; Pluck and Brown, 2002).
Alzheimer's disease	~50%	Along with PD probably has had the greatest level of research interest to date, including epidemiology, imaging correlates (reviewed below) and therapeutics (Lanctôt et al., 2017).
Frontotemporal dementia	>50% (particularly behavioural variant)	A core feature of behavioural variant FTD (which can have different underlying pathologies) although also present in other subtypes. Strongly associated with impulsivity (Lansdall et al., 2017).
Progressive supranuclear palsy (PSP)	Up to 90%	Occurs in nearly all patients with PSP, a parkinsonian condition associated with predominantly subcortical tau pathology (Litvan et al., 1996)
Corticobasal syndrome (CBS)	50-90%	A common feature of this neurodegenerative syndrome, which is associated with different underlying pathologies (Litvan et al., 1998)
Huntington's disease	>30%	Common and strongly related to disease progression (Thompson et al., 2012; van Duijn et al., 2014)
Traumatic brain injury	20-72%	Increasingly recognised as a sequalae(Arnould et al., 2013)
HIV Infection	25-40%	A common sequelae of HIV infection, it is related to extent of brain pathology particularly within ventral striatum and subcortical white matter (Castellon et al., 1998; Hoare et al., 2010; Paul et al., 2005).
Multiple sclerosis	22%	Emerging evidence suggests apathy is a common neurobehavioural feature of MS (Rosti-Otajärvi and Hämäläinen, 2013)
Myotonic dystrophy	40%	A noted feature of this condition, although limited research to date (Rubinsztein et al., 1998)
Wilson's disease	24%	Noted in some patients in a single study (Svetel et al., 2009)

1.1.2.1 Cerebral small vessel disease

Cerebral small vessel disease (SVD) occurs secondary to pathological changes within small arteries supplying the deep structures of the brain (Pantoni, 2010).The resultant progressive background damage – often with superimposed discrete events (lacunar

infarcts or cerebral microbleeds) – leads to a range of problems including cognitive decline and dementia, gait disturbance and neuropsychiatric sequalae (Briley et al., 1997; Prins et al., 2005; Staekenborg et al., 2010). Vascular disease risk factors (many of which are modifiable) such as hypertension underlie the development of SVD, which therefore becomes more prevalent with increasing age (Basile et al., 2006). Whilst most SVD occurs sporadically, a genetic form caused by mutations in the NOTCH 3 gene and associated dysfunction of vascular smooth muscle cells exists (Chabriat et al., 2009; Joutel et al., 1996). This disease, cerebral autosomal dominant arteriopathy with subcortical ischaemia and leukoencephalopathy (CADASIL) is characterised by extensive damage to white matter brain regions from chronic subcortical ischaemia. It provides a monogenic model of SVD, developing at a significantly younger age, and in the setting of fewer comorbid conditions, than sporadic SVD (Chabriat et al., 2009).

Apathy is an increasingly recognised feature of both sporadic and genetic cerebral small vessel disease (Ligthart et al., 2012; Reyes et al., 2009). A recent study identified apathy in 28% of patients with imaging-confirmed sporadic SVD (Lohner et al., 2017), whilst prevalence in CADASIL is estimated at approximately 40% (Reyes et al., 2009). As such, apathy is now viewed as one of the cardinal features of CADASIL (Chabriat et al., 2009).

1.1.2.2 Parkinson's disease

Parkinson's disease (PD) is a common neurodegenerative disorder characterised by both motor and non-motor deficits, in which a central dopaminergic deficit is a defining feature (Kalia and Lang, 2015). Apathy is common at all stages of the disease, with prevalence estimates ranging from 17 – 70% (depending on specific populations and scales used), a figure which is likely to lie around 33% in the general PD population (Aarsland et al., 2009; Dujardin and Defebvre, 2012; Pluck and Brown, 2002).

1.1.3 Clinical accompaniments of apathy in SVD and PD

Cognitive dysfunction

Although it can occur at any stage of the disease, both SVD and PD patients with apathy are more likely to show cognitive dysfunction than their non-apathetic counterparts (Aarsland et al., 2009; Lohner et al., 2017; Pluck and Brown, 2002; Reyes et al., 2009). In general the methods for assessing cognition have been quite non-specific (for example the Mini Mental State Examination), however some recent work suggests that it is deficits in so-called executive functions (including sequencing, planning and information processing speed) which are more likely to be associated with apathy (Lohner et al., 2017).

Depression

Apathy and depression are dissociable syndromes in both SVD and PD, but nonetheless can occur together (Aarsland et al., 2009; Hollocks et al., 2015; Pluck and Brown, 2002; Reyes et al., 2009). Both apathy and depression may result from dysfunction of a number of different underlying neurobiological systems, and indeed recent efforts have been made to ground research on neuropsychiatric disorders within these putative cognitive systems (Holroyd and Umemoto, 2016). The syndrome of depression can be broadly broken into dysphoric (sadness) and anhedonic (loss of pleasure) symptoms (Treadway and Zald, 2011). Furthermore, anhedonia has been further broken down into *liking* (consummatory enjoyment) and *wanting* (motivation to pursue rewarding outcomes). It is within this latter construct of a wanting deficit that depression and apathy are most likely to overlap neurobiologically (Treadway and Zald, 2011). Apathy and depression have also been dissociated on epidemiological grounds in longitudinal studies of SVD. Whilst apathy develops in a "dose-dependent" manner depending on the number of cardiovascular risk factors a patient has at baseline, the same temporal relationship does not seem to exist for depression (Newson et al., 2010; van der Mast et al., 2008)

Reduced quality of life

In both SVD and stroke apathy has been associated with reduced quality of life, poorer health outcomes and reduced engagement in good health practices (Caeiro et al., 2012;

Hollocks et al., 2015; Mayo et al., 2009). In PD, the negative impact of apathy on both patients and their families/carers has also been demonstrated (Aarsland et al., 2009). A striking example of this was reported in a recent study of PD patients undergoing deep brain stimulation (DBS) for treatment of their motor symptoms. Following the procedure, those without apathy at baseline experienced a significant improvement in quality of life, whilst those with apathy did not, despite showing the same degree of improvement in motor symptoms (Martinez-Fernandez et al., 2016). These studies illustrate the deleterious effects of apathy on a patient's global well-being, emphasising the importance of understanding its mechanisms and developing effective treatments.

1.1.4 Apathy treatments

A broad range of pharmacological and non-pharmacological strategies have been trialled as apathy treatments. These studies have often been small and observational, or single case studies (Chase, 2011). A few randomised controlled trials have been completed, including of dopamine agonists (Chung et al., 2016; Thobois et al., 2013), cholinesterase inhibitors (Devos et al., 2014) and methylphenidate (Rosenberg et al., 2013), however at this stage there is insufficient evidence to make strong recommendations about specific apathy treatments.

1.1.5 Summary

Apathy is a debilitating disorder of motivation resulting in reduced goal directed behaviours, which commonly accompanies a range of neurological conditions. No clearly effective treatments exist, in part because understanding of its underlying causes is lacking. Apathy manifests in a strikingly similar way across diverse underlying pathologies, suggesting that a common cognitive mechanism may underlie its development. Before considering such a mechanism, it is worth reviewing the concepts of motivation and goal directed behaviour – two terms intrinsically linked to the apathetic syndrome.

1.2 Motivation and goal directed behaviour

1.2.1 Motivation

The word motivation derives from the Latin word *movere,* meaning to move. The common use of the term today generally refers to the presumed underlying explanation for an organism's behaviour (or movement). It is a concept central to the understanding of ourselves and the world, and as such has intersected with prominent schools of philosophical thought, in particular determinism which broadly holds that all behaviours have antecedents, or causes (Hoefer, 2016).

In more recent times, constructs of motivation have tended to emphasise the presumed internal processes – whether they be hard-wired drives (metabolic, sexual) or more flexible cognitive processes – that underlie observable behaviour (Berridge, 2004; Salamone and Correa, 2012). As scientific study has focussed on the neural mechanisms by which internal (e.g. homeostatic states) and external (e.g. goals) factors are integrated to produce motivated behaviour, a more specific description of motivation has evolved. Whilst defining motivation broadly as *the set of processes through which organisms regulate the probability, proximity and availability of stimuli,* Salamone and Correa identify core features of motivated behaviour (Salamone and Correa, 2012). It can be divided into two phases. Firstly, an appetitive or instrumental phase, characterised by actions towards (or away from) a reinforcing positive (or negative) stimulus, which are executed with a certain level of energy (vigour) over time (persistence). Secondly, a consummatory, hedonic phase where the organism interacts with the target stimulus. A broad literature now demonstrates the dissociability of these two phases on both anatomical and neuromodulatory grounds (Berridge, 2004; Salamone and Correa, 2012; Treadway and Zald, 2011). A simple and useful distinction is that the appetitive phase is akin to *wanting* (how hard you will work, with how much vigour and for how long) whereas the consummatory phase is akin to *liking* (enjoyment of the reinforcer) (Berridge and Kringelbach, 2015; Treadway and Zald, 2011).

Therefore, motivation may be best thought of as a psychological construct that encompasses the underlying reasons and processes that explain behaviour directed towards or away from environmental stimuli. However as I discuss in the next section,

modern psychology distinguishes different *types of behaviour* which can be described as motivated.

1.2.2 Goal directed behaviour – defining features

Current definitions of apathy generally contain reference to a disruption of goal directed behaviour (Levy and Dubois, 2006; Robert et al., 2009). However, there is now a reasonable consensus in the psychology/neuroscience literature that multiple forms of behaviour exist. These systems are separable, with different underlying anatomical substrates, learning processes, neurotransmitter influences and computational structures (Daw and O'Doherty, 2014).

The three main systems are Pavlovian, habitual and goal directed. The Pavlovian system is based on a *Stimulus-Outcome* mapping – environmental stimuli become associated with positive or negative outcomes, without reference to the actions required to achieve them. The Pavlovian response is inflexible, however differs from a simple reflex in that it can be predictive about *future* salient biological events. In contrast, both habitual and goal directed behaviours are *instrumental* – that is they are based on an association involving an action (or response). Habitual (or stimulus-response) systems learn whether an action results in a better or worse than predicted outcome, forming stronger and weaker stimulus-response associations. In contrast, goal directed systems explicitly represent the *action-outcome contingency* – that is the costs and consequences (positive or negative) associated with an action – as well as accounting for the *current outcome value* for an organism (Balleine and O'Doherty, 2010).

While computing the action-outcome contingency allows goal directed behaviours greater flexibility (for example stopping feeding behaviour immediately when sated), this comes at an increased metabolic and time cost, and in many situations a habitual (stimulus-response driven) approach is more adaptive. The precise mechanism by which these and the Pavlovian systems interact and control behaviour is an on-going research question (de Wit and Dickinson, 2009). All systems involve reciprocally connected basal ganglia-cortical connections, and are innervated by dopaminergic projections, a neurotransmitter thought to play a crucial role in both learning and activation of

behaviours (Balleine and O'Doherty, 2010; Daw and O'Doherty, 2014) – see **Dopamine, decision making and apathy**.

Apathy is conceptualised as a disorder of *goal directed behaviour* (Levy and Dubois, 2006), and this thesis focuses on aspects of this system – particularly the interplay between rewarding outcomes of actions and the action costs themselves. However it should be noted that there is little (if any) evidence to show that either habits or Pavlovian responses are preserved (or otherwise) in patients with apathy.

Viewing apathy as a disorder of goal directed behaviour is a useful step in delineating its underlying mechanisms, however this term remains broad, encompassing many cognitive processes whose disruption could theoretically reduce motivated behaviour. To focus investigations on potentially relevant systems, I now consider the growing neuroimaging literature that links apathy to changes in specific anatomical regions. By then focusing on the components of motivated goal directed behaviour these implicated regions are crucial for, I develop a hypothesis about the underlying cognitive mechanisms of the apathetic syndrome that forms the basis for the empirical chapters of this thesis.

1.3 Neuroanatomical correlates of apathy across neurological conditions

One of the tools that has been used to explore apathy across a broad range of disorders – including neurodegenerative, traumatic, infectious and genetic conditions – has been neuroimaging. A wide variety of brain imaging techniques has now been employed to probe differences in brain structure and connectivity, perfusion and metabolism, as well as functional properties of specific brain regions. Here, I review studies using such approaches that have reported on anatomical markers of apathetic states (Le Heron et al., 2017).

1.3.1 Parkinson's disease

1.3.1.1 Altered metabolism in PD apathy

A number of studies using fluorodeoxyglucose positron emission tomography (FDG-PET) have been conducted in patients undergoing deep brain stimulation (DBS) as a treatment for their PD. The occurrence of apathy after DBS surgery has led to much interest due to the opportunity it provides for potentially understanding the anatomical basis of such effects. In one of the largest and best controlled studies published to date, Robert et al performed FDG-PET *pre-operatively* in 44 PD patients, and correlated activity with *post-operative* change in apathy scores. Decreased metabolism within the right ventral striatum (VS) predicted the development of apathy post-operatively, when controlling for the confounding effects related to the DBS stimulation and other medications (Robert et al., 2014). In non-DBS PD groups, apathy is also associated with altered metabolism within medial frontal brain regions – specifically anterior cingulate cortex (ACC) and orbitofrontal cortex (OFC) bilaterally – as well as temporo-parietal changes (Huang et al., 2013).

Whilst FDG-PET estimates general metabolic activity (and presumably underlying neuronal loss), research using more specific metabolic imaging techniques has implicated dopaminergic neuromodulatory systems in the development of apathy in PD. Apathetic PD patients have reduced dopamine and/or noradrenaline receptor binding capacity within bilateral VS (Remy et al., 2005). They have reduced striatal dopamine binding capacity even at the time of PD diagnosis, and *before* they have commenced dopaminergic therapy (Santangelo et al., 2015). Furthermore, following administration of methylphenidate they show blunted dopamine release in ACC, OFC, dorsolateral prefrontal cortex (DLPFC), left posterior cingulate cortex (PCC), right temporal cortex and left subcortical regions (particularly thalamus and globus pallidus interna (GPi)), consistent with dopaminergic denervation of these areas (Thobois et al., 2010).

Finally, in a task-based FDG-PET study that hints at the functional significance of these changes, patients with apathy had lower activation of ventromedial prefrontal cortex

(vmPFC), striatum, amygdala and midbrain than non apathetic patients when making *actions for incentives compared to no incentives* (Lawrence et al., 2011). The midbrain is the site of the ventral tegmental area (VTA), a key source of dopaminergic projections to the nucleus accumbens (NAc, within VS) and to prefrontal cortex. As I discuss in detail later, a core function of these brain regions might be to represent the *value* of potential actions. The blunted incentive-related activity observed in this study suggests altered reward processing in PD patients with apathy may be a consequence of these metabolic changes.

1.3.1.2 Structural changes associated with apathy in PD

Fewer studies have been performed using magnetic resonance imaging (MRI), but the pattern of results is in line with investigations using FDG-PET. Using a recently developed technique for estimating the three dimensional shape of subcortical structures, investigators found that apathetic individuals had greater atrophy within the NAc and dorsolateral head of caudate, with the strongest result in left NAc (Carriere et al., 2014). In contrast, the authors found no association between *cortical thickness* and apathy status. This is consistent with the largest study to date investigating brain morphology and apathy in PD which found no association between grey matter (GM) volume and apathy status (Baggio et al., 2015). It is worth noting that an earlier study had reported an association between increasing apathy severity and reduced GM volume in a number of brain regions, including anterior and posterior cingulate gyri, insula and lateral inferior frontoparietal regions (Reijnders et al., 2010). However, only a small proportion of patients in this investigation were clinically apathetic.

1.3.1.3 Functional connectivity is altered in PD apathy

Whilst the metabolic and structural imaging techniques discussed above allow assessment of localised brain regions, complex goal directed behaviour relies on an interactive, distributed network of brain areas. Functional connectivity analysis of resting state functional MRI (fMRI) data provides one estimate of such connections, measuring the correlation of changes in blood oxygen level dependent (BOLD) signal between separate regions. It can be constrained by limiting analyses to brain regions that are anatomically connected. Baggio and colleagues first used probabilistic tractography

to parcellate the striata into regions based on *structural* white matter connectivity with anatomically defined frontal brain areas. They then assessed *resting-state* connectivity between these defined subcortical-cortical areas, and correlated this measure with apathy severity. They reported functional connectivity of frontostriatal circuits was reduced in apathetic cases, specifically affecting connections between medial frontal brain areas (encompassing regions of OFC and ACC) and connected striatal areas (Baggio et al., 2015). These findings are in broad agreement with an earlier, smaller study, which also demonstrated apathy was associated with medial frontal resting state fMRI differences, albeit using a different analysis technique (Skidmore et al., 2013).

1.3.1.4 Summary – neuroimaging in PD apathy

Neuroimaging studies of apathy in PD have implicated VS and dACC, together with regions in medial and lateral prefrontal cortex and the midbrain area that contains the key dopaminergic VTA. All of these regions are interconnected. Furthermore, there are monosynaptic dopaminergic projections from the VTA to each of the frontal regions implicated (Williams and Goldman-Rakic, 1998). Such widespread involvement of brain regions modulated by dopamine perhaps makes it unsurprising that apathy is so prevalent in PD, a disorder which primarily affects dopaminergic systems. But as I discuss below, apathy is also very common across a range of brain disorders that traditionally have not been attributed to dopaminergic deficits.

1.3.2 Small vessel disease and stroke

1.3.2.1 Imaging correlates of apathy in patients with small vessel disease

SVD tends to affect subcortical and deep white matter regions of the brain (Pantoni, 2010). From a neurobiological perspective it is important to understand whether apathy is associated with disruption of particular white matter tracts, or whether it is simply a more general effect of widespread cerebral damage. A recent large study of sporadic SVD addressed this question using diffusion MRI. Apathy was associated with reduced FA within WM pathways including the anterior cingulum, uncinate fasciculus and fornix (Hollocks et al., 2015). These white matter tracts link brain regions such as ACC and VS which are strongly implicated in the development of apathy in other conditions

(Kos et al., 2016; Le Heron et al., 2017). Interestingly, a single study in CADASIL (genetic SVD) patients has demonstrated apathy is associated with morphological changes in these same medio-frontal and orbitofrontal brain areas (Jouvent et al., 2011), changes that have presumably occurred as a result of disruption of underlying white matter tracts.

Intriguingly, SVD may also be an important modulator of apathy in other neurodegenerative conditions. This is illustrated by two large studies of people with different dementia diagnoses. Apathy was associated with the presence of both white matter hyperintensities (Jonsson et al., 2010) and lacunar infarcts within deep WM (Lavretsky et al., 2008). Additionally, within AD patients, even after excluding lacunar infarcts (and therefore many subjects who likely had SVD), Starkstein et al still found the presence of apathy was associated with greater *frontal* WMH volume (Starkstein et al., 2009).

1.3.2.2 Imaging correlates of apathy in patients following stroke

Stroke (ischaemic or haemorrhagic) provides one of the closest comparisons to lesion models in animal work utilized to understand motivated behaviour (reviewed below), albeit with the caveat that background variability in subclinical apathy levels limits the possibility to draw strong conclusions about causality. Nevertheless, apathy following stroke provides an important opportunity to understand the neurobiology of this syndrome. A meta-analysis examining the relationship between stroke and apathy found no lateralizing effects of hemisphere involvement on apathy occurrence, but this study did not attempt to delineate specific brain regions in which apathy was more likely to occur (Caeiro et al., 2013). In fact, the authors actively excluded a number of investigations (summarized below) that have specifically examined this association, to avoid biasing their sample.

Subcortical strokes can occur in the context of SVD, or by separate mechanisms. Basal ganglia lesions, particularly those involving the caudate nucleus or nucleus accumbens, have been associated with the development of apathy (Bhatia and Marsden, 1994; Gerace et al., 2013; Maeda et al., 2012; Phillips et al., 1987). Profound apathy is also seen following lesions to the GPi, a crucial output structure of the basal ganglia (Adam

et al., 2013). A number of studies report apathy occurring following infarction of the thalamus – specifically paramedian or anterior regions (Engelborghs et al., 2000; Ghika-Schmid and Bogousslavsky, 2000; Krolak-Salmon et al., 2000; Nishio et al., 2011; Perren et al., 2005), reviewed by (Carrera and Bogousslavsky, 2006). Limited reports link cerebellar and brainstem involvement with post stroke apathy (Hoffmann and Cases, 2008).

The classical cortical stroke location linked to apathy is medial frontal cortex, within the vascular supply of the anterior cerebral artery (ACA). In 100 consecutive ACA territory strokes apathy developed in 43% percent of patients, and was significantly more likely to occur if the lesion included medial regions (frontal pole, cingulate gyrus) or superior frontal gyrus (Kang and Kim, 2008).

Finally, apathy can complicate strokes in other cortical locations (Caeiro et al., 2013). This might be a direct consequence of damage to the brain region, or due to diaschisis of connected regions. Lesions outside the frontal lobes have been associated with altered frontal metabolism (measured using MR spectroscopy of the frontal poles) in apathetic compared to non-apathetic patients (Glodzik-Sobanska et al., 2005). Similar evidence for the disruption of frontal functional networks is provided by an in-depth case study of a single patient who developed apathy following multiple small embolic infarcts. Despite structural imaging demonstrating the ACC was not primarily affected by the emboli, the patient had reduced functional connectivity (assessed using resting state fMRI) within the cingulo-opercular network, providing further evidence of the occurrence of apathy associated with frontal network dysfunction *at a distance* (Siegel et al., 2014). One study has in fact concluded that cerebral blood flow within the basal ganglia is reduced in apathetic compared to non-apathetic patients, irrespective of stroke location (Onoda et al., 2011). And a recent report of patients who had suffered ischemic stroke used diffusion-based MR imaging and graph theory analysis to estimate structural white matter connectivity between different brain areas and derive a network associated with apathy. The authors demonstrated that reduced connectivity in many regions remote from the stroke, including the same frontal and basal ganglia regions outlined above, was associated with apathy (Yang et al., 2015).

1.3.2.3 Summary – neuroimaging in SVD and post-stroke apathy

Apathy is a recognized feature of strokes that affect portions of the medial frontal cortex including the ACC and OFC, subcortical areas including nucleus accumbens, ventral pallidum, caudate nucleus, and medial thalamic nuclei, and disruption of the white matter tracts that connect these regions. Although apathy also commonly occurs in association with more distant brain lesions, some evidence suggests that this may be mediated by alterations within the same fronto-striatal structures implicated above.

1.3.3 Alzheimer's disease and other neurodegenerative conditions

1.3.3.1 Altered metabolism and perfusion

FDG-PET studies have demonstrated that apathy in Alzheimer's disease (AD) is associated with reduced metabolism in OFC and ACC, as well as VS, medial thalamus and some temporal regions (Holthoff et al., 2005; Marshall et al., 2007; Schroeter et al., 2011). These results are generally similar to analogous studies in PD, and highly concordant with investigations that have used single-photon emission computed tomography (SPECT) imaging to measure regional cerebral blood flow (which is closely coupled to underlying neuronal metabolism). Research using SPECT has consistently demonstrated that reduced perfusion in ACC and OFC – as well as frontopolar and DLPFC regions in some studies – is associated with apathy in AD (Benoit et al., 2004; Craig et al., 1996; Lanctôt et al., 2007; Migneco et al., 2001; Robert et al., 2006). Strikingly, when regional metabolism or perfusion is examined *across different disorders* (including frontotemporal dementia (FTD) and subjective cognitive impairment in one study, and AD and organic personality disorder in another), apathy is strongly correlated with reduced ACC activity (Migneco et al., 2001; Schroeter et al., 2011). Furthermore, by controlling for the presence of other behavioural disturbances associated with regional hypometabolism, one group has identified that hypometabolism in the VTA is specifically associated with apathy, across dementia diagnoses (Schroeter et al., 2011).

1.3.3.2 Structural changes

As with PD, there is variability in the results of studies examining GM changes and apathy in AD. This is at least in part a reflection of differing inclusion criteria, image acquisition, and analysis techniques. Two well conducted studies – using different analysis methods – identified atrophy within ACC, DLPFC, putamen and caudate nucleus was associated with apathy in patients with AD (Bruen et al., 2008; Tunnard et al., 2011). Similarly, in a large study including patients with AD, FTD, PSP and CBS, the presence of apathy correlated with reduced GM volume in ACC, OFC, middle frontal gyrus, anterior insula and caudate (Rosen et al., 2005). Furthermore, reduced GM volume in ACC and insula was found in apathetic patients with PSP or AD (N = 17 of each condition, Stanton et al., 2013). There was no interaction between diagnosis and apathy in this analysis, suggesting the observed changes were a shared feature of apathy in both conditions. Two smaller studies limited to patients with FTD also reported apathy was associated with atrophy in similar regions to the above work, albeit with less robust corrections for multiple comparisons (Eslinger et al., 2012; Zamboni et al., 2008). In contrast to these results, two other investigations of more than 50 patients did not find an association between apathy and GM volume in AD (Kim et al., 2011; Starkstein et al., 2009).

A few studies using diffusion imaging to assess white matter tract integrity have been carried out in these conditions. In a population with mild AD, apathy was associated with reduced fractional anisotropy (FA) in the left anterior cingulum, but no other regions (Kim et al., 2011). A single study in patients with PSP identified damage to corpus callosum, uncinate fasciculus and superior longitudinal fasciculus was associated with apathy (Agosta et al., 2014).

1.3.3.3 Summary – AD and other neurodegenerative conditions

A wide range of neuroimaging techniques have been used to investigate neural correlates of the apathetic syndrome in neurodegenerative conditions, particularly AD. Altered functional and structural properties of medial frontal cortex, especially ACC and OFC, are the most robustly identified cortical changes associated with apathy, whilst subcortically alterations in ventral striatum, medial thalamus and VTA are the

strongest associations. It is notable that implicated white matter tracts connect these neural regions.

1.3.4 Huntington's disease

Although apathy is an important feature of Huntington's disease (HD) (Thompson et al., 2012), the few imaging studies investigating its correlates have been notable for the absence of positive results. A large study (N=240) in pre-symptomatic and early HD did not find any associations between apathy and either GM or WM changes (Scahill et al., 2011). However, because only individuals with early disease were studied, the rates and severity of apathy were very low, and the imaging markers used are also likely less sensitive to early changes than functional approaches. Similarly a diffusion imaging study of 80 patients from another (early stage) demographic, albeit with a greater range of apathy scores, failed to find an association between apathy and white matter integrity (Gregory et al., 2015). In contrast, a single, smaller investigation reported apathy negatively correlated with FA in the bilateral rectus gyrus white matter, an area containing fibres connecting OFC and subcortical structures including VS (Delmaire et al., 2013).

1.3.5 Traumatic Brain Injury

In a heterogeneous group of 60 patients who had suffered traumatic brain injury (TBI), reduced volume within brain regions including medial frontal cortex was associated with greater severity of apathetic features (Guild and Levine, 2015). Another small study of 10 apathetic TBI patients reported that volume loss in the left hippocampus strongly correlated with apathy (Takayanagi et al., 2013). Overall, evidence for the neuroimaging correlates of apathy in TBI is limited, and further research is required to determine whether the associations described for other conditions are also true for this complex entity.

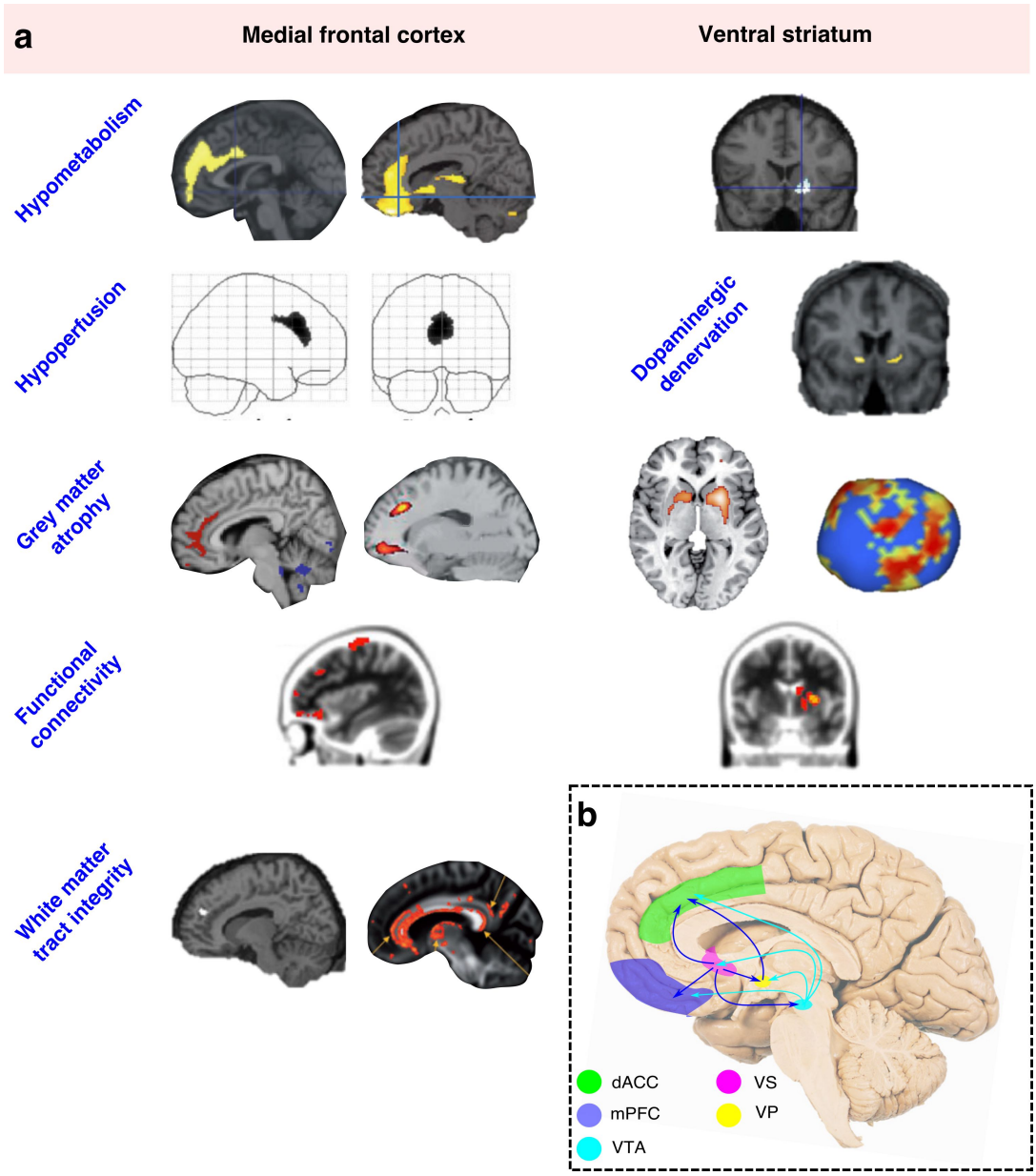


Figure 1-2. Consistent anatomical associations with apathy across imaging modalities and underlying disorders

(**a**) Changes affecting dorsal anterior cingulate cortex and ventral striatum are particularly prominent, with multiple techniques used in studies including patients with Parkinson's disease, Alzheimer's disease, Huntington's disease and SVD. (**b**) A connected system of brain areas consistently associated with apathy, which form an interconnected network within the medial forebrain.

dACC – dorsal anterior cingulate cortex; mPFC – medial prefrontal cortex; VTA – ventral tegmental area; VS – ventral striatum; VP – ventral pallidum.

Images (from top left) adapted from (Schroeter et al., 2011*;* Huang et al., 2013*;* Robert et al., 2014*;* Migneco et al., 2001*;* Remy et al., 2005*;* Stanton et al., 2013*;* Bruen et al., 2008*;* Carriere et al., 2014*;* Baggio et al., 2015*;* Ota et al., 2012*;* Hollocks et al., 2015*;* Marshall et al., 2007).

1.3.6 Human immunodeficiency virus infection

Apathy in human immunodeficiency virus (HIV) infection is associated with reduced NAc volume (Paul et al., 2005). As is evident in other disorders, there is also disruption of frontal white matter tracts in apathetic individuals with HIV. Two studies have demonstrated apathy is associated with reduced FA within the genu of corpus callosum, anterior thalamic radiation and superior/anterior corona radiata – tracts that connect medial frontal cortex and subcortical regions (Hoare et al., 2010; Kamat et al., 2014). Although limited in scope, the imaging correlates of apathy in HIV infection are consistent with changes observed in other conditions, particularly those observed in ventral striatum.

1.3.7 Summary: common neuroimaging changes associated with apathy across disease category

Across a range of underlying pathologies, and despite variations in design, neuroimaging studies that have investigated the anatomical correlates of apathy converge on a consistent pattern **Figure 1-2**. Broadly, apathy is associated with disruption of frontostriatal circuits, but in particular the ACC and OFC cortically, and subcortical structures including the VS, medial thalamus and VTA, or connections between these regions. These associations are demonstrated across techniques that measure underlying neuronal metabolism, grey matter atrophy, and both structural and functional connectivity. Whilst ACC and VS are identified most consistently across disorders, other regions are also implicated less regularly. Interestingly these regions, including insula, DLPFC and OFC are mono-synaptically connected with each other, and also to the ACC and VS. This suggests that disruption to the wider circuitry connected to ACC and VS may also be linked to apathy.

Overall, disruption of these structures – particularly ACC and VS – is a unifying feature across the majority of studies. This suggests a strong anatomical basis for the disrupted goal directed behaviour that defines the apathetic syndrome. In the next section I review the anatomical and functional properties of these brain regions, as they relate to normal

motivated behaviour. I then discuss the potential functional significance of these brain regions for apathy, developing specific hypotheses that are tested within this thesis.

1.4 The neuroscience of effort-based decision making

As outlined above, a core feature of goal directed behaviour is the explicit representation of an action-outcome contingency (Balleine and O'Doherty, 2010). This representation, which involves integrating potential costs of an action with its predicted (rewarding) outcomes to guide choice describes the essence of effort-based decision making (Kurniawan et al., 2011; Rushworth et al., 2011). In this section I present evidence that the core components of effort-based decision making are instantiated neurally within particularly anterior cingulate cortex and ventral striatum, suggesting this cognitive system may be crucial to the development of apathy (Le Heron et al., 2017).

1.4.1 The ACC – ventral striatal – VTA loop

Functional anatomy

Classical accounts suggest the basal ganglia nuclei form closed loops with cortical areas via the pallidum, leading to the notion of distinct frontostriatal circuits (Alexander and Crutcher, 1990; Haber et al., 1993). Such proposals have since been shown to be too simplistic as it is now clear that these loops are not isolated, but also connect to some extent to each other through both cortical and subcortical regions. Nevertheless, there is strong evidence that neurons in the VS have monosynaptic projections to the ventral pallidum (VP), and this same part of the VP projects to the dorsal and ventral bank of the dorsal anterior cingulate sulcus (Haber et al., 1995, 1993; Vogt, 2009; Yeterian and Pandya, 1991). These same ACC regions project back to the core and shell of the nucleus accumbens and neighbouring regions of the VS (Vogt, 2009; Yeterian and Pandya, 1991). Notably, both the ACC and VS also receive strong, monosynaptic inputs from dopaminergic neurons in the VTA (Haber and Knutson, 2010). The dopaminergic system is strongly linked to motivated behaviour, reward processing and overcoming effort costs (Haber and Knutson, 2010; Hamid et al., 2016; Salamone and Correa,

2012). Thus, VS and ACC are connected in a closed loop via VP, and receive strong dopaminergic inputs from the VTA.

Effects of experimental lesions

The components of the ACC-VS-VTA loop are likely to have similar functional properties, and therefore damage to any of these regions may result in similar behavioural consequences. There is now a wealth of literature demonstrating that structural lesions to either the ACC or VS, or to the white matter tracts connecting them, reduces the willingness of animals to engage in effortful actions for reward (Floresco and Ghods-Sharifi, 2006; Hauber and Sommer, 2009; Rudebeck et al., 2006; Walton et al., 2002 - Figure 3a). In a classic example, structural ACC lesions biased rodents away from a previously preferred high effort, high reward option, towards a low effort, low reward option (Walton et al., 2002). Crucially, animals remained sensitive to the magnitude of reward on offer, choosing the high reward option consistently when effort costs are equalised. Therefore, ACC damage made animals unwilling to exert high effort for high reward outcomes, without changing the hedonic value of the reward. This suggests ACC (and also, from similar experiments, VS) lesions interfere with the instrumental (wanting) phase of motivated behaviour, without affecting consummatory (liking) aspects.

Complimentary to these experiments demonstrating the effects of structural lesions, a significant body of literature has also found similar behavioural changes associated with pharmacological lesions. In particular, blocking dopamine's action within VS consistently reduces animals' willingness to exert effort for reward (Salamone et al., 2007, 1994). More recently, similar effects have also been demonstrated with antagonism of other neuromodulatory systems, including serotonin (5-HT_{2C} receptors Bailey et al., 2016), acetylcholine (Fobbs and Mizumori, 2014) and adenosine (A_{2A} (Nunes et al., 2013). Interestingly, current understanding of the functional anatomy of these systems suggests they exert their effects on effort-based decision making via interactions with the mesolimbic dopaminergic system (Salamone et al., 2016).

Summary

The VS and ACC, strongly associated with apathy across neurological disorders, form a strong functional loop which, when lesioned structurally or pharmacologically, reduces

the willingness of animals to engage in effortful behaviour for reward, without interfering with their hedonic response to rewarding outcomes. In addition to the results of these lesion studies, the last decade of neuroscientific research has greatly increased understanding of the mechanisms by which the cost benefit evaluations which underlie normal motivated behaviour are instantiated within in particular ACC and VS, and these are reviewed in the next section.

1.4.2 "*Is it worth it*?" The cost benefit evaluation in effort-based decision making

Valuation of effort and reward in the ACC and VS

Conceptually, at the heart of an effort-based decision lies the question "is the current behaviour being evaluated worth it"? Whilst many background factors contribute to this (**Figure 1-3**), cognitive neuroscience has placed emphasis on the ultimate comparison, weighing the costs of an action against its predicted rewarding outcomes (Rushworth et al., 2012). Research suggests that this decision is made by ascribing a numerical value to exerting effort to obtain rewards. The cost of exerting effort devalues the potential reward on offer (Trevor Chong et al., 2017a; Hartmann et al., 2013; Klein-Flugge et al., 2016). Neuroimaging studies in healthy human adults have consistently implicated the dACC and VS in signalling the effort costs of a particular behaviour, but also in signalling rewards on offer prior to any action being performed (Apps and Ramnani, 2014; Botvinick et al., 2009; Croxson et al., 2009; Schmidt et al., 2012; Vassena et al., 2014). Neurophysiological recordings from macaque monkeys have also identified neurons in the ACC, the firing of which relate to cues that predict rewards on offer as well as effort costs required (Kennerley et al., 2009). The ACC and VS are therefore sensitive to effort and reward related information *preceding* performance of a behaviour. Thus these regions are well placed to evaluate the cost and benefits of exerting effort, and indeed activity of some ACC neurons correlates with an integration of these two key factors (Kennerley et al., 2009 - **Figure 1-4b**).

It is worth noting that prior to, or in parallel with representations within VS and ACC, both effort and reward information are also encoded within other connected brain regions – brain regions which have also been associated with apathy in some studies. The anterior insula (which has extensive reciprocal connections to the ACC) is thought

to encode a relatively raw effort cost signal (Croxson et al., 2009; Skvortsova et al., 2014). In contrast, evidence suggests that the lateral OFC integrates incoming sensory information with previous associations/memories to predict rewarding outcomes (Padoa-Schioppa and Assad, 2008). However to guide choice amongst options with disparate outcomes (e.g. drinking a cup of coffee or going for a run), economic theories have long postulated the existence of a common scale for representing value. A number of studies have suggested ventromedial prefrontal cortex (vmPFC) and medial OFC play such a role, and a recent metanalysis identified a small region within these areas in which neural activity parametrically varies with subjective value of multiple different reward types (Levy and Glimcher, 2012). These medial prefrontal areas are also extensively connected to both ACC and subcortical structures including VS (Haber and Knutson, 2010).

Integrating cost-benefit information to drive behaviour

A number of reports suggest vmPFC, ACC and VS are crucial for integrating this combined cost/benefit information to a value signal that drives subsequent behaviour (Floresco, 2015; Kennerley et al., 2009; Klein-Flugge et al., 2016; Rushworth et al., 2012). It is also within these regions that value signals can be integrated with other internal and external signals that influence an individuals' motivational state, including homeostatic signals, affective state and external pressures (Mogenson et al., 1980). It is this interplay that is thought to culminate (or not) in an action, as well as determining the vigour with which it is performed (Hamid et al., 2016; Kolling et al., 2016; Mogenson et al., 1980; Varazzani et al., 2015) **Figure 1-3**.

Recent work has begun to examine the neural mechanisms that guide these decisions of whether it is worth exerting effort. Some fMRI studies have required people to make choices between different 'offers' which vary in terms of the reward on offer and also the amount of effort required. Using computational modeling of the choices each person makes, researchers quantify the extent to which each individual is devaluing rewards by the required effort. Such models provide an estimate of the subjective value (*SV*) of exerting effort for reward. That is, they can examine how much value is ascribed to each effort-reward combination and thus how motivated an individual is to choose to put in effort for a reward. Using this approach several investigations have now shown that the ACC and VS signal *SV* of exerting effort for reward, a computation that is considered to

be important in guiding motivated behaviour (Burke et al., 2013; Chong et al., 2017; Klein-Flugge et al., 2016; Kurniawan et al., 2010; Massar et al., 2015; Scholl et al., 2015; Skvortsova et al., 2014). Furthermore, these regions seem to play a domain-general role in processing effort costs, showing sensitivity to effort regardless of whether it is physical or cognitive (Chong et al., 2017 - **Figure 1-4c**).

Interestingly activity in ACC and VS is relatively specific to effort costs. Other costs that influence the subjective value of a reward such as temporal delay and risk are dissociable from effort, and are processed in other regions of the frontal lobe (Burke et al., 2013; Massar et al., 2015; Prevost et al., 2010; Rudebeck et al., 2006). It is also important to note that the role of ACC and VS in effort-based decision making is not limited to valuation of rewards and effort costs and the subsequent decision to act. Rather, evidence suggests they also play a crucial role in determining the vigour with which to pursue an action (Niv et al., 2007), sustaining motivation towards a goal across an extended series of behaviours (Holroyd and Yeung, 2012), evaluating whether a behaviour is worth persisting with (Kolling et al., 2016), and monitoring the outcomes of actions to update expectations for subsequent situations (Hauser et al., 2017; Scholl et al., 2015) - **Figure 1-4 d-f**.

Summary

Consistent with the behavioural outcomes of lesion work described in the previous section, growing evidence demonstrates that human ACC and VS, along with other interconnected brain regions, play crucial roles in valuing and motivating choices that will result in the exertion of effort. This work suggests that effort-based decision making may provide a fruitful neurobiological framework for understanding the mechanisms of apathy. However there is also growing evidence that signals in both ACC and VS are modulated by the value of a chosen action during sequences of actions, as well as crucially the value of alternatives and other properties of the environment. This evidence has been part of a shift in the conceptualisation of effort-based decision making, from standard economic models of binary choice, to a more ecologically derived opportunity cost framework – a framework which is well described by foraging theories of behaviour and may be directly relevant to how we view the apathetic syndrome. The science of foraging decisions is reviewed in the next section.

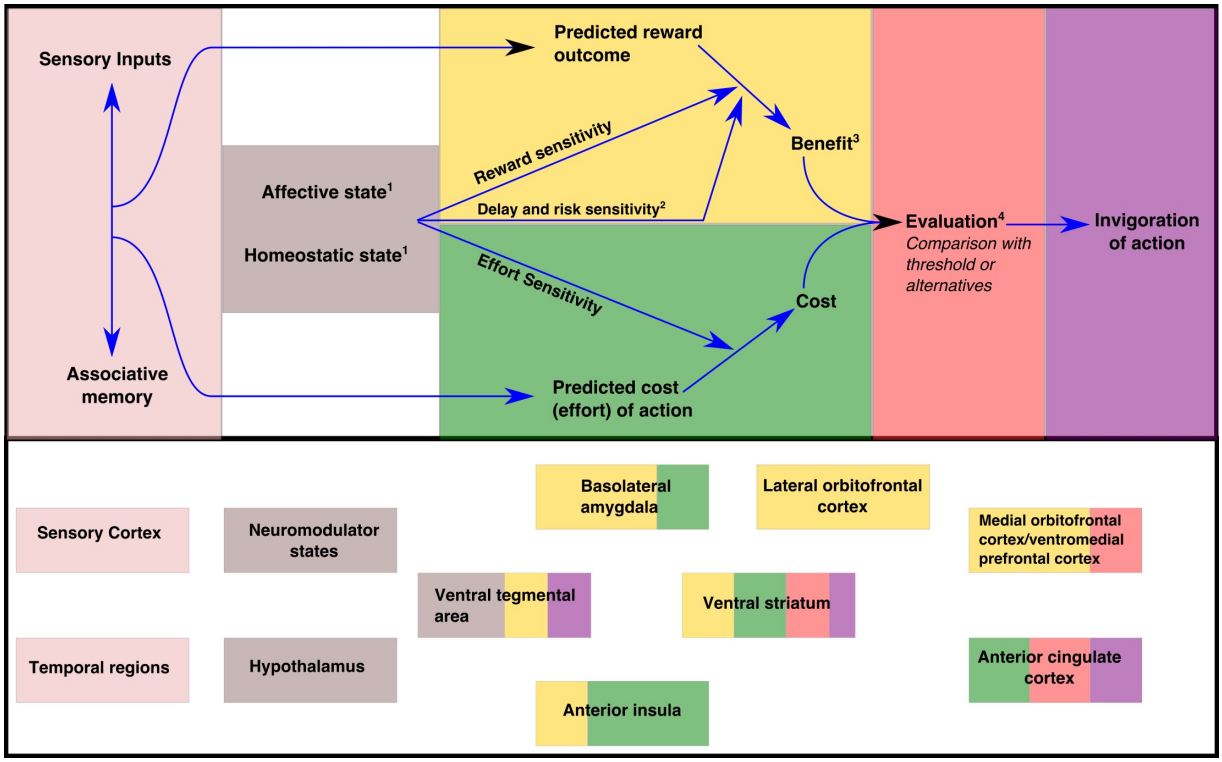


Figure 1-3. Deciding to act – a framework

A distributed network of brain regions contributes to an *action-outcome* representation and subsequent evaluation and invigoration of behaviour.

1. These factors, including neuromodulator levels, network dynamics and hormonal factors combine to form a 'motivational state' that influences the representation of costs and benefits, depicted as *'sensitivity'* to these components.
2. Delay and risk 'costs' impact directly on reward value, rather than being evaluated as an action cost.
3. This is the *subjective* value of the outcome of action
4. Evaluation can occur in serial fashion ("is this option worth engaging with") or by comparing across action-outcome representations (parallel evaluation).
5. Other regions, including globus pallidus interna, medial thalamus, premotor and motor cortex also contribute to this network.

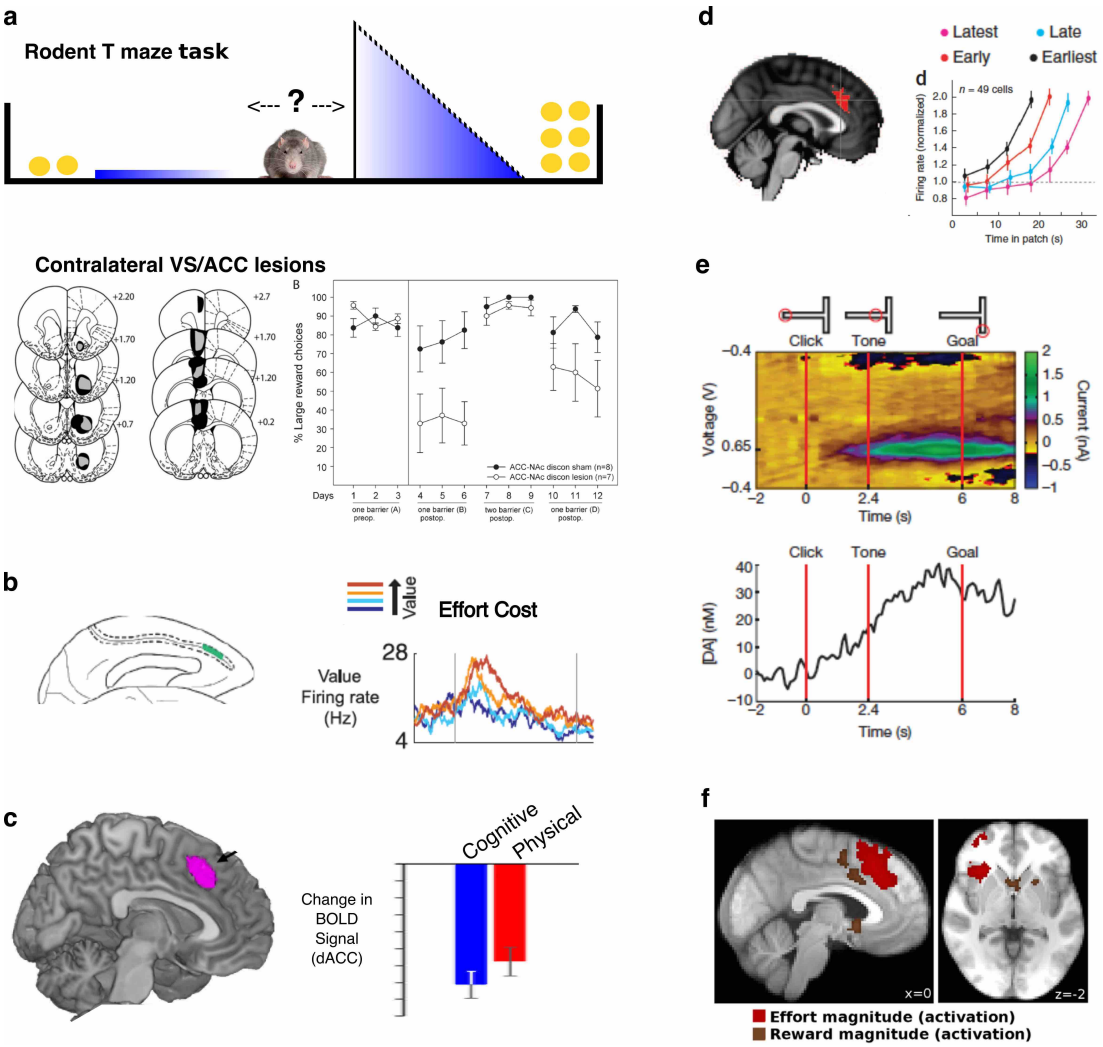


Figure 1-4. Importance of ACC and VS for motivated behaviour

Effort based decision making. Lesions to ACC, VS or crossed ACC/VS disconnection lesions (pictured) cause rodents to choose more low effort/low reward options, without altering their preference for high rewards options if effort costs are equal **(a)** (*from Hauber and Sommer, 2009)*. Single neurons within macaque ACC modulate firing rates to the net value of a choice (reward – effort) **(b)** *(from Kennerley et al., 2009*). BOLD activity within human ACC signals the subjective value of a choice (reward – effort), whether the cost is physical or cognitive **(c)** *(from Chong et al., 2017)*.

Modulating behaviour to foreground and background environment characteristics. BOLD activity correlates with the value of foraging (switching from current option), rather than the value of the actual chosen option **(d – left panel)** *(from Kolling et al., 2012)*. Single neuronal recordings from the ACC of macaques performing a patch leaving foraging task show earlier increases in firing rate on trials where the animal leaves the patch faster **(d – right panel)** *(from Hayden et al., 2011)*.

Sustaining behaviour towards a goal. Recordings from rodent VS show ramping dopamine signals as the animal approaches a rewarding outcome, thought to drive persistence of behaviour towards the goal **(e)** *(from Howe et al., 2013)*.

Monitoring outcomes of actions. ACC and VS activity encodes information on both reward and effort magnitudes during the outcome phase of an action **(f)** *(from Scholl et al., 2015)*.

1.4.3 Foraging theory – a framework for effort-based decision making?

As animals and humans negotiate their environment, they constantly solve complex decision making problems that involve weighing up the benefits of potential actions against the costs of these actions (Balleine and O'Doherty, 2010; Kolling et al., 2016; Kurniawan et al., 2011; Rushworth et al., 2012). Much of the understanding of effort-based decision making processes reviewed above has been derived from studies in which participants – whether rodent, non-human primate or human – made decisions between discreet, often binary options (e.g. option 'a' versus option 'b'). However real-world decision makers must evaluate options within their current environmental context (Pearson et al., 2014; Stephens and Krebs, 1986). Foraging theories (so-called because of the ecological behaviours they have traditionally described) present this problem as a foreground vs background structure – that is, *what am I doing right now* vs *what else could I be doing?* Importantly, there is accumulating evidence in both humans and animals that the brain regions particularly associated with apathy – ACC and VS – encode and integrate these foreground and background variables to drive behaviour (Hayden et al., 2011; Kolling et al., 2012).

Optimal foraging theory and the patch leaving problem

Optimal foraging theory is a class of models developed to parameterise and describe naturalistic animal behaviour (Stephens et al., 2007; Stephens and Krebs, 1986). A crucial problem encountered by a foraging animal is the *patch leaving problem*. Simply, when an animal is harvesting rewards from one location (patch), they generally deplete over time. This means the instantaneous return drops the longer they remain at that location. At any point, they can leave this location to move to a new one, however this leaving decision incurs costs of time and energy (to reach the next patch). When should an animal move on from their current patch? Assuming a forager makes decisions to maximise their overall energy gain, the solution to the patch leaving problem is described elegantly by the Marginal value theorem (MVT) (Charnov, 1976; Stephens and Krebs, 1986) – **Figure 1-5.** The MVT states that a forager maximises their overall energy intake by leaving each patch when the instantaneous reward rate (i.e. their harvest in the current time-step) in that patch drops below the background environmental average reward rate. This background rate can be thought of as the

opportunity cost of the current (foreground) behaviour – what is the foraging animal missing out on by persisting with their current action?

The Patch Leaving Problem

When to move on?

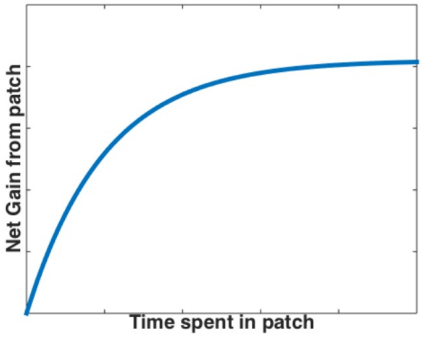




Costs to leave patch:
Time
Energy

Next patch

Current patch, in which reward (gain) rate decreases over time



A representative patch gain function. Typical patches have negatively decelerated gain functions, meaning the gain rate reduces the longer is spent in a patch.

The Marginal Value Theorem (MVT) describes the mathematically optimal solution to the patch leaving problem, assuming the forager aims to *maximise their long-term net rate of energy gain.*

1. In the most general situation, reward rate (**R**) is equal to net energy gains (reward from patch - energetic costs, ***E***) divided by time costs (delay between patches, **d**; and time spend in each patch, **t**)

$$R = \frac{E}{d + t} \quad (1)$$

2. When more than one patch-type exists (e.g. three types of flower), eqn (1) can be expressed as (2):
Here, for the *ith* patch type:

$$R = \frac{\Sigma \lambda_i g_i(t_i) - k_i}{d_i + \Sigma \lambda_i t_i} \quad (2)$$

R = overall reward rate in this environment

λ = encounter rate with this patch type

g(t) = the patch gain function - the energy gained after spending **t** time in the patch

t = patch residence time - *the foraging decision variable*

k = energetic costs associated with foraging

d = travel time between patches

3. It can be easily demonstrated that **R** is maximised (the presumed foraging goal) when the derivative of R (with respect to time) is equal to zero:

$$R'(t) = 0 \quad (3)$$

4. Differentiating (2) with respect to time, substituting (3) into the answer, and rearranging gives (4). This result demonstrates that the average reward rate (**R**) is maximised by choosing a patch residency time (**t**) such that the foreground reward rate **g'(t)** is equal to the background average reward rate (right side of eqn 4).

Implications:

1. For a given environment, foragers should leave their current patch when the instantaneous reward rate (the marginal rate) drops to the background average reward rate - however this patch residency time will vary depending on each patch gain function.
2. Increasing travel time between patches (**d**) will reduce the background reward rate and therefore the optimal marginal rate at leaving, resulting in longer patch residency times.
3. Increasing energy costs (**k**) will also reduce background reward rate and result in longer patch residency times
4. Increasing the proportion of patches with high-yielding gain functions (**g(t)**) will increase the background reward rate and therefore reduce patch residency time in all patch-types.

$$g'_i(t_i) = \frac{\lambda_i g_i(t_i) - k_i}{d_i + \lambda_i t_i} \quad (4)$$

Foreground instantaneous reward rate = **Background environment reward rate**

Figure 1-5. Patch leaving and the marginal value theorem.

For a more detailed discussion of these factors, see (Stephens and Krebs, 1986)

Foraging behaviour in the wild and the lab

A rich behavioural ecology literature exists describing the behaviour of animals in naturalistic and laboratory-based settings in terms of optimal foraging theory (Stephens et al., 2007). A plethora of studies involving animals from across the kingdom have demonstrated that behaviour can be modelled *as if* these animals are tracking the variables central to the marginal value theorem (Charnov, 1976; Krebs et al., 1977; Nonacs, 2001; Pyke, 1978; Stephens et al., 2007; Stephens and Krebs, 1986). A number of anthropological studies have suggested that human hunter-gather behaviour also follows the predictions of optimal foraging theory (Aswani, 1998; Metcalfe and Barlow, 1992; Smith et al., 1983), although it has been noted these observations represent qualitative, rather than quantitative evidence for human foraging behaviour (Hutchinson et al., 2008).

In fact, very little work has investigated the mechanisms of human patch leaving behaviour, and results have been discordant. Hutchinson et al reported that simple heuristics (e.g. leave after a certain number of trials) explained the behaviour of healthy participants better than foraging models, as they completed a patch leaving task. However this conclusion may, at least in part, have been related to the nature of the paradigm used, in which background environments had high variability and reward presentation within patches occurred only intermittently (Hutchinson et al., 2008). These features may have favoured simpler decision strategies, and limit the generalisability of these findings. In contrast, a recent study which used computational methods to assess learning within a patch leaving framework found that foraging models provided a closer account of participant behaviour than traditional reinforcement learning (temporal difference) models (Constantino and Daw, 2015). This task manipulated travel time between patches (which were apple trees, with each tree returning decrementing numbers of apples with each 'forage'), the quality of each patch (starting number of apples in a tree) and the rate at which they depleted. However, because of the focus on learning, participants were never at 'steady state' from an information perspective, which violates a central assumption of foraging theory – that a forager has complete information. Therefore, no systematic study of human patch leaving behaviour has been carried out, and it remains unclear whether human decision makers are sensitive to the predictions of the MVT.

Neural mechanisms of foraging behaviour – crucial roles for ACC and VS

A prediction of the MVT is that, to make optimal decisions, animals should track and compare foreground and the background reward rates to determine the value of leaving. A landmark paper by Hayden and colleagues demonstrated for the first time that neuronal firing within macaque ACC encoded such a patch leaving decision variable (Hayden et al., 2011). The authors used a paradigm in which macaques made sequential decisions about whether to remain in their current patch (in which they received juice drops of decreasing volume) or move on to the next one (where the volume of juice delivered would initially return to the maximum), incurring a cost of time to 'travel' between the patches during which they received no juice. The firing rate of these ACC neurons increased at each successive decision to *stay* in a patch, until it reached a threshold that corresponded to behavioural patch leaving. Furthermore, increasing travel time to the next patch resulted in both reduced gain of these firing rates, and an increase in the firing rate threshold to patch leave. Together these observations are consistent with foraging animals computing a decision variable that corresponds to the relative value of leaving a patch – a variable that is compared to a threshold that, once surpassed, triggers patch leaving behaviour. Intriguingly, some evidence also exists for a similar process in human decision makers. Neural activity (as measured by changes in BOLD signal) within this same brain region (dACC) in participants performing a related type of foraging task tracked the value of 'foraging' (rejecting an offer to search for a better one) (Kolling et al., 2012). As with the macaque study, participants' behavioural decisions to forage were predicted by this dACC signal. Finally, a prominent theory in cognitive neuroscience holds that tonic levels of dopamine within the VS signal background environmental reward rates, and therefore the opportunity costs of actions (Niv et al., 2007). Early work is beginning to investigate the significance of this signal in the context of foreground/background decision making (Hamid et al., 2016)

Summary

Foraging theories of decision making emphasise a comparison between foreground and background reward contexts, explain animal behaviour in naturalistic and experimental settings, and neurally may be instantiated within the same brain regions in which damage is associated with apathy in humans. However, many important questions remain to be answered, including whether human decision makers are sensitive to the

variables of the marginal value theorem, and the role of neuromodulators such as dopamine in foraging decisions.

1.4.4 Dopamine, decision making and apathy

Finally, before considering what implications the normal functions of ACC and VS have for our understanding of apathy, I review work which links the neuromodulator dopamine to these systems and apathetic behaviour.

Dopamine and effort-based decision making

The dopaminergic system is closely associated with reward, value and action representations (Hamid et al., 2016; Kurniawan et al., 2011; Niv et al., 2007). This system projects from the midbrain ventral tegmental area and substantia nigra pars compacta to ventral and dorsal regions (respectively) of the basal ganglia, and medial (particularly dorsal ACC) and lateral frontal cortical regions in reciprocal loops (Haber and Knutson, 2010). Dopamine projections from the ventral tegmental area (VTA) to in particular VS and medial frontal cortex (often described as the mesolimbic dopaminergic system) play a crucial role in effort based decision making (Kurniawan et al., 2011). The dominant view of the dopaminergic signal as it pertains to effort-based decision making is that it encodes the value of potential actions to drive appetitive/approach behaviours for reward (Hamid et al., 2016; Kurniawan et al., 2011; Salamone and Correa, 2012; Syed et al., 2016). Consistent with this view, the experimental administration of dopaminergic antagonists, either systemically or intra-accumbens, reduces the willingness of rodents to exert effort for reward, without changing the hedonic value of rewarding outcomes in the absence of effort costs (Bailey et al., 2016a; Salamone et al., 2007, 1994). Similarly in humans, dopamine administration increases the effort participants will exert for a given reward (Chong et al., 2015; Le Bouc et al., 2016).

Traditionally, dopaminergic signals have been considered as phasic and tonic (Niv et al., 2007; Schultz and Dickinson, 2000), although recent work has suggested a more integrative view, with, for example, phasic release influencing tonic levels (Hamid et al., 2016). Nevertheless, the two signals differ in their speed of onset and action, and

have been associated with different effects in the neuroscientific literature. A large body of work suggests the phasic dopamine signal encodes reward and effort prediction errors within particularly VS and ACC (Hauser et al., 2017; Schultz, 2007), whilst others have interpreted aspects of this consistently elicited response as a more general salience signal (Redgrave and Gurney, 2006). Still another related, but separate theory holds that phasic dopamine release within VS signals 'cue-triggered wanting' – the motivational or incentive salience of a perceived stimulus (Berridge, 2012).

Less evidence exists for the role of tonic dopamine, however, as mentioned earlier, a current prominent theory holds that it encodes information about the background reward rate in the environment, and thus the opportunity cost of an animal's current action. This theory predicts that as environmental reward rate (and therefore dopamine levels) increase, animals should act with greater vigour because each chosen behaviour carries a greater cost in terms of foregone rewards – a prediction for which there is reasonable evidence (Hamid et al., 2016; Niv et al., 2007). This raises intriguing, but unanswered questions about the role tonic dopamine levels may play in foraging decisions, which emphasise a comparison with exactly this sort of environmental background reward rate.

Dopamine and apathy

Much of the evidence linking apathy and dopamine comes from Parkinson's disease. Although PD has been traditionally associated with degradation within the nigrostriatal dopaminergic pathway, it is clear that the mesolimbic system is also affected, and reasonable evidence links denervation within this to the occurrence of apathy. Apathetic patients show reduced VS dopamine binding capacity, as well as blunted dopamine release following administration of methylphenidate, compared to PD patients without apathy (Remy et al., 2005; Santangelo et al., 2015; Thobois et al., 2010). Furthermore, a randomised controlled trial of the dopamine D2/3 agonist Piribedil for treatment of apathy following deep brain stimulation (and reduction of normal dopaminergic medications) demonstrated an improvement in apathy (Thobois et al., 2013), although this result was not replicated in a more recent study using a different dopamine agonist (Chung et al., 2016). There are also case reports of improvement in apathy symptoms in other neurological conditions with the administration of dopamine agonists (Adam et al., 2013; Kohno et al., 2010).

In all, whilst dopamine clearly exerts important effects on normal motivated behaviour, the precise relationship between the dopaminergic system and apathy remains unclear – particularly whether the disruption in goal directed behaviour that defines the apathetic syndrome occurs along the same axis as the mesolimbic dopaminergic system exerts its effects.

1.5 Disrupted effort-based decision making – a cognitive mechanism for amotivated behaviour?

In the above sections I have presented evidence that apathy, conceptualised as a disorder of goal-directed behaviour, is consistently associated with damage or disruption to medial frontal cortical structures and subcortical regions, particularly anterior cingulate cortex and ventral striatum, across a range of neurological disorders. These neural regions play a crucial role in motivated behaviour. They integrate the costs of actions with their rewarding outcomes to drive goal directed behaviour – a process often termed effort-based decision making – and are strongly influenced by the mesolimbic dopaminergic system. Experimental disruption of these areas, whether structurally or pharmacologically, reduces the willingness of animals to engage in effortful actions for reward, mirroring the apathetic phenotype.

I therefore propose that disrupted effort-based decision making is an important cognitive mechanism underlying apathy. There is some additional evidence to support this hypothesis.

Apathy in Parkinson's disease has been associated with impaired incentive processing, with apathetic patients showing reduced autonomic and electrophysiological responses to reward. In the former study, the authors measured the degree to which a participant's pupils dilated in response to a verbal stimulus informing them how much reward was on offer in the next trial. The normal increase in dilatation as rewards increase was blunted in apathetic patients (Muhammed et al., 2016). In the latter work, the investigators used EEG to record the feedback related negativity (FRN) in Parkinson's disease patients performing a gambling task. The FRN response, which is thought to arise within ACC, was significantly blunted in apathetic patients compared to non-apathetic patients and

healthy controls which the authors interpreted as consistent with impaired incentive processing (Martinez-Horta et al., 2014a). However neither of these studies examined decision making based on weighing up the effort required to obtain a particular reward, and thus it is unclear what the behavioural implications of these reduced responses are.

Despite its high prevalence, no mechanistic studies of apathy have been performed in sporadic or genetic SVD. A single study in the post-stroke setting found patients with apathy showed reduced saccadic velocity towards rewards, interpreted as a reduction in reward sensitivity (Rochat et al., 2013). In the psychiatric literature, increased sensitivity to effort costs has been associated with the apathy component of the negative symptoms of schizophrenia (Hartmann et al., 2015), while a sample of patients with major depressive disorder showed reduced willingness to exert effort for reward in a different behavioural paradigm, a result the authors reported was linked to the anhedonic components of depression (Treadway et al., 2012). Additionally, apathetic traits in healthy young people have been associated with altered effort-based decision making in a study that also mapped to these changes to individual differences in ACC and supplementary motor function (Bonnelle et al., 2016). To my knowledge, no studies have investigated a link between foreground/background decision making and apathy traits.

In sum, early work suggests the utility of conceptualising apathy as a disorder of effort-based decision making, but evidence, particularly in neurological disorders where apathy is a common and debilitating problem, is lacking. In this thesis, I identify five questions related to the hypothesis that disrupted effort-based decision making underlies apathy in patients with neurological disorders, and investigate them empirically in patients with CADASIL and Parkinson's disease, as well as healthy young and elderly people.

1.5.1 Does disrupted effort-based decision making underlie apathy in patients with neurological diseases? And are changes driven by increased sensitivity to the costs of actions or reduced sensitivity to the rewarding outcomes of actions?

I investigate these questions in two separate disorders – CADASIL and Parkinson's disease – using an accept/reject effort-based decision making task and both raw and computational analysis of patient choices (**Chapters 2 and 4**). In both studies non-apathetic patients serve as a disease-matched control group, along with an age and gender match healthy control population. Participants make trial by trial decisions about whether to accept or reject offers of reward (money) in return for exerting physical effort. A computational analysis of their choices allows the relative influence of changing reward and effort costs to be estimated and compared between apathetic and non-apathetic patients.

1.5.2 Do specific changes in effort-based decision making (insensitivity to the rewarding outcomes of actions) in apathetic patients map onto related physiological markers of reward processing? And do these patients show changes in structural connectivity between the neural regions that underlie this process?

Analysis of the decision making paradigm used in the CADASIL group (**Chapter 2**) gives us a quantifiable estimate of an individual's sensitivity to changes in effort and reward – that is, the behavioural consequence of changes in these variables. I use a separate task to measure autonomic (pupillary) responses to changing incentives in the same CADASIL patients, in order to compare this physiological marker of reward sensitivity to the subjective marker derived from patients' own choices (**Chapter 3**). I then use diffusion MRI methods in these same patients to investigate whether specific changes in white matter integrity (the dominant site of pathology in CADASIL) in regions connecting the core brain areas underlying normal effort-based decision making (reviewed above) are associated with the apathetic state, and with behavioural and physiological changes in incentive processing.

1.5.3 Do changes in effort-based decision making in apathetic patients occur along the same, or a separate mechanistic axis to dopamine depletion?

As outlined above, there is strong evidence linking the dopaminergic system to the willingness to exert effort for reward, and some evidence implicating disrupted dopamine signalling in Parkinson's disease apathy, suggesting this condition may be mediated by changes in dopaminergic tone. However, recent work has also suggested an important role for other neuromodulatory systems in effort-based decision making. To investigate the relationship between apathy, dopamine and effort-based decision making, I administer the decision making task mentioned above to apathetic and non-apathetic patients with Parkinson's disease, ON and OFF their normal dopaminergic medications (**Chapter 4**). I specifically focus on the regions of decision space (reward/effort combinations) in which apathy and dopamine exert their predominant effects.

1.5.4 Are healthy human decision makers performing a patch leaving foraging task sensitive to the factors specified in the marginal value theorem? And does their degree of sensitivity correlate with underlying apathy traits?

Foraging decision problems provide a more ecological framework within which to study effort-based decision making, and therefore may be crucial to our understanding of the apathetic syndrome. However little work has been done to investigate whether theories that describe foraging behaviour in animals, such as the marginal value theorem, also apply to humans. In **Chapter 5** I develop a novel patch leaving task which independently manipulates the key variables specified in the MVT, and systematically test whether healthy human decision makers are sensitive to these factors. I then investigate whether the degree of sensitivity to these variables (including effort and delay costs, and background and foreground reward information) correlates with baseline apathy traits.

1.5.5 Is patch leaving behaviour altered in patients with apathy? Or by changes in dopaminergic tone? Specifically, are apathetic patients impaired in their ability to use background reward information to decide when to move on from their current activity? And do changes in dopamine levels alter behaviours that depend on estimating background environmental reward rates?

Results in earlier chapters suggest that apathy is associated with alterations in reward processing, such that patients are not incentivised by the rewarding outcomes of their actions. As outlined above, foraging decisions emphasise a comparison between foreground and background reward rates to guide behaviour. Tonic dopamine levels have been proposed to signal these background reward rates. Do apathetic patients show reduced goal directed behaviour because they underestimate background reward rates, meaning it never seems worth switching to a new activity? Do changes in dopaminergic tone shift the influence of environmental context on patch leaving? And how do changes in dopamine tone interact with motivational state? In **Chapter 6** I investigate these questions using a novel patch leaving task in which foreground and background reward rates are independently manipulated. The task is administered to two populations – healthy elderly participants ON and OFF a single dose of the dopamine agonist Cabergoline, and apathetic and non-apathetic PD patients, ON and OFF their normal dopaminergic medications, as well as matched controls.

1.6 Specific research methods

1.6.1 Questionnaire methods to assess apathy

Lille Apathy Rating Scale

The scale was first developed for use in the Parkinson's disease population (Sockeel et al., 2006), however has subsequently been validated and used in other conditions including schizophrenia, frontotemporal dementia and Alzheimer's disease (Fernández-Matarrubia et al., 2017; Yazbek et al., 2014). It involves a semi-structured clinical interview – lasting approximately 10 minutes – and provides both quantitative scores

and a good sense of a person's daily life, activities and motivational levels. The LARS also contains four subscales – termed *intellectual curiosity, emotion, action initiation and self-awareness*.

Apathy Evaluation Scale

I also administered the Apathy Evaluation Scale (self-report) given its widespread use to assess apathy across a range of disorders over the last 3 decades (Clarke et al., 2007; Marin et al., 1991). Additionally the use of two scales improved the sensitivity of our apathy diagnosis, given concerns for potentially missing the diagnosis when using patient-rated scales (Radakovic et al., 2015).

See **Appendix 1** for full questionnaires.

1.6.2 Questionnaire methods to assess other relevant domains

Depression

I assessed depression primarily using the Beck's depression inventory II (BDI-II) (Beck et al., 1996). As well as being a widely validated scale, it can be split into a dysphoria-only subscale which allows apathy and depression to be more easily dissociated (Kirsch-Darrow et al., 2011). I have also administered the shorter geriatric depression scale (GDS) because it has been used extensively within the SVD apathy literature (Hollocks et al., 2015; Ligthart et al., 2012; van der Mast et al., 2008).

Quality of life

Quality of life was assessed using a Cantril ladder (Cantril, 1965) and, in the CADASIL group, the WHO-5 well-being index (Topp et al., 2015).

See **Appendix 1** for full questionnaires.

1.6.3 Additional cognitive tasks

As a general cognitive screen I administered the Addenbrooke's cognitive examination III, a commonly used clinical tool which assesses attention, memory, verbal and

categorical fluency, language and visuospatial domains during an approximately 10-15 minute assessment (Hsieh et al., 2013). Given previous work suggesting cognitive deficits in CADASIL particularly involve so-called executive functions, I also included a digit span working memory task (Groth-Marnat, 2000), the Trail Making Task parts A and B (Tombaugh, 2004), and a Design Fluency task, in which participants were required to generate as many novel designs by connecting up to 5 dots with straight lines in a two minute period (Tucha et al., 2012).

1.6.4 Assessment of physical signs

CADASIL patients were examined for physical impairments using the National institute of health stroke scale (NIHSS - Brott et al., 1989). PD patients were assessed using the United Parkinson's Disease Rating Scale, part III (UPDRS-III - Goetz et al., 2008).

2 Mechanisms of apathy in CADASIL

2.1 Chapter Summary

In this chapter I test the hypothesis that disrupted effort-based decision making is associated with apathy in patients with cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), using a behavioural paradigm within which the effects of effort on choice can be dissociated from those of reward. The results demonstrate a clear change in behaviour in the apathetic group, with these patients accepting fewer offers across the experiment. Complementary analysis techniques demonstrate this effect is driven by reduced incentivisation by the rewarding outcomes of actions, rather than by the effort costs of actions. The results provide evidence that effort-based decision making is altered in CADASIL patients with apathy, and demonstrate a cognitive mechanism by which these behavioural changes might occur.

2.2 Introduction

As its name suggests, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is a monogenetic disorder, caused by mutations within the NOTCH-3 gene and characterised by extensive damage to white matter brain regions (Chabriat et al., 2009; Joutel et al., 1996). This damage is thought to result from dysfunction of vascular smooth-muscle cells within small arteries, leading to chronic subcortical ischaemia and gradually accumulating pathological brain changes (Chabriat et al., 2009). CADASIL is considered an excellent model of the vastly more common sporadic cerebral small vessel disease (SVD). The younger age of CADASIL patients means that they have fewer co-morbidities and easily identifiable pathology, unlike sporadic SVD cases who can frequently also have Alzheimer pathology (Charlton et al., 2006; Gold et al., 2007).

Apathy, a disorder of motivated behaviour, is one of the cardinal symptoms of CADASIL, manifesting in at least 40% of patients (Reyes et al., 2009). It is also a

common complication of sporadic SVD, with prevalence estimates close to 30% (Lohner et al., 2017). Intriguingly, evidence suggests that the presence of cerebral SVD may also modulate the development of apathy in other neurological conditions, including Alzheimer's disease and stroke (Brodaty et al., 2013; Jonsson et al., 2010; Lavretsky et al., 2008; Starkstein et al., 2009). In CADASIL, it has been associated with disease and imaging severity, but can occur at any stage (Reyes et al., 2009). Apathetic patients are more likely to be depressed, but as in other conditions, a number of patients have apathy without depression, indicating these constructs are dissociable (Pluck and Brown, 2002; Reyes et al., 2009; van der Mast et al., 2008). The importance of apathy is underlined by the significant impact it has on the well-being of patients and their families (Caeiro et al., 2012; Hollocks et al., 2015; Mayo et al., 2009). However its underlying mechanisms remain poorly understood and no effective treatments exist.

Apathy has been conceptualised as a disorder of goal directed behaviour (Levy and Dubois, 2006; Marin, 1991). The defining feature of goal directed behaviour is the formation of an action-outcome representation – a representation relating the costs of an action to its predicted rewarding outcomes (Balleine and O'Doherty, 2010).
This process of weighing up action costs against rewards to guide choice is often referred to as effort-based decision making (Kurniawan et al., 2011; Rushworth et al., 2011). Intriguingly the neural regions that sub-serve this process – including anterior cingulate cortex (ACC), orbitofrontal cortex (OFC) and ventral striatum (VS) – are the same regions that have been associated with apathy across neurological conditions (Chong et al., 2017; Croxson et al., 2009; Hauser et al., 2017; Klein-Flugge et al., 2016; Kos et al., 2016; Le Heron et al., 2017; Prevost et al., 2010). Furthermore, animal models of effort-based decision making have causally linked damage to both ACC and VS with behavioural changes that resemble the clinical phenotype of apathy. Lesions to these regions induce a seemingly apathetic state in animals, in which they are no longer as willing to invest effort for reward (Hauber and Sommer, 2009; Salamone et al., 1994; Walton et al., 2002). Crucially, animals in these experiments remain sensitive to the magnitude of reward on offer, choosing the high reward option consistently when effort costs are equalised. This behavioural observation resonates with the phenomenological description apathetic patients offer when asked about their reduced activities, frequently reporting *"I just can't be bothered"*, or *"it doesn't seem worth it"* (personal observation).

A number of studies in SVD have found an association between apathy and global burden of vascular disease (e.g. volume of white matter hyper-intensities – WMH) (Hollocks et al., 2015; Jonsson et al., 2010; Kim et al., 2013; Lavretsky et al., 2008). Importantly however, a recent study in sporadic SVD demonstrated that changes in fractional anisotropy (FA, a measure of white matter integrity) within the anterior cingulum, uncinate fasciculus and fornix were associated with apathy (Hollocks et al., 2015). These white matter tracts link the brain regions strongly implicated in the development of apathy in other conditions (Kos et al., 2016; Le Heron et al., 2017). Furthermore, in a single imaging study of CADASIL patients apathy was associated with morphological changes in these same mediofrontal and orbitofrontal brain areas (Jouvent et al., 2011). Therefore, there is some evidence to suggest that the neuroanatomical correlates of apathy in SVD are similar to other neurological disorders, consistent with the idea that disruption of a common cognitive system may underlie apathy across underlying pathologies (Le Heron et al., 2017).

Here I tested the hypothesis that effort-based decision making is altered in CADASIL patients with apathy, using non-apathetic CADASIL patients as well as matched healthy participants as controls. Specifically, I predicted that:

1) Apathetic patients would be less willing than non-apathetic patients to engage in effortful behaviour for rewards
2) This change in behaviour would be driven by either
    a. Increased sensitivity to the effort costs of actions
    b. Reduced sensitivity to the rewarding outcomes of actions

I tested these predictions using a novel effort-based decision making paradigm that dissociated the effects of reward and effort on choice. I used a computational model of choice to estimate the quantitative impact of these variables in each patient, as they decided whether or not to engage in each offer. Furthermore, in the following chapter, I use these estimates to relate behaviour to physiological measures of the effort-based decision making process.

2.3 Methods and Materials

2.3.1 Ethics

This study was approved by the local ethics committee and written consent was obtained from all subjects in accordance with the Declaration of Helsinki.

2.3.2 Participants

Nineteen patients with a genetically confirmed diagnosis of CADASIL were recruited from two regional specialist centres (in Cambridge and Oxford, UK). Patients were excluded from the study if they had physical disability such that they would be unable to squeeze a hand-held dynamometer (one person), or had a previously documented large vessel territory stroke (no people). Patients with a history of lacunar stroke (3 people) were included because this is an intrinsic feature of CADASIL, and is also a cardinal feature of sporadic SVD (Chabriat et al., 2009; Pantoni, 2010). 19 healthy age and gender-matched controls were recruited via a local database.

2.3.3 Apathy Definition

Apathy was assessed using the Lille Apathy Rating Scale (LARS), (Sockeel et al., 2006). To improve sensitivity of the diagnosis, the Apathy Evaluation Scale (AES) self-report was also administered (Clarke et al., 2007; Marin et al., 1991). Apathy was diagnosed if either the Lille apathy rating scale (LARS) score was > -22 *or* the Apathy Evaluation Scale score was > 37 (equivalent to at least mild-moderate apathy).

2.3.4 Measures of disease severity, cognition and mood

Physical symptoms/signs were assessed using the National Institutes of Health Stroke Scale (Lyden, 2017). Patients were screened for the presence of cardiovascular risk factors and common sequalae of CADASIL (Migraine, previous stroke, depression) and

all medications were noted. Baseline cognitive levels were formally assessed using the Addenbrookes's Cognitive Examination III (Hsieh et al., 2013). Given previous work suggesting cognitive deficits in CADASIL particularly involve executive functions, a digit span working memory task (Groth-Marnat, 2000), the Trail Making Task parts A and B (Tombaugh, 2004), and a design fluency task in which participants were required to generate as many novel designs by connecting up to 5 dots with straight lines in a two minute period (Tucha et al., 2012) were also administered.

Depressive symptoms were assessed using the Geriatric Depression Scale (GDS) which has been the most extensive index used in SVD apathy research ((Hollocks et al., 2015; Ligthart et al., 2012; van der Mast et al., 2008). Fatigue was assessed using the 9-item Fatigue Severity Scale (FSS) (Valko et al., 2008). Quality of life was assessed using a Cantril Ladder (Cantril, 1965), in which subjects rated their overall current quality of life on a visual scale ranging from one to ten, and the WHO-5 Well-being Index (Topp et al., 2015).

2.3.5 Experimental design

Participants were administered an effort-based decision making task. They were seated in front of a desktop computer running Psychtoolbox (psychotoolbox.org) implemented within Matlab (MathWorks, USA). They registered their responses using one of two handheld dynamometers (SS25LA, BIOPAC Systems, USA), which were calibrated to each individual at the beginning of the session. Each participant's maximal voluntary contraction (MVC) was calculated separately for each hand, defined as the maximum force exerted over three maximal contractions. All subsequent responses were thus normalised to each individual.

On a trial-by-trial basis, participants were given sequential offers of reward in return for exerting effort **Figure 2-1a**. Each offer was presented on the screen as a cartoon apple tree. Reward on offer for the current trial was indicated by the number of apples on the tree (1, 3, 6, 9, 12 or 15) and was also numerically displayed underneath the tree. Each apple was worth 1p. Effort required to obtain the reward was indicated by the height of the yellow bar on the tree trunk, with the six possible levels corresponding to 10, 24, 38,

52, 66 and 80% of a participant's MVC **Figure 2-1b**. The six reward and effort levels were systematically combined and the resultant 36 conditions were sampled evenly in a pseudo-randomised order across five blocks, for a total of 180 trials **Figure 2-1c**. This meant all participants received the same offers, presented in the same order.

Participants were instructed to weigh up the effort costs against the reward on offer for each trial, and decide *"if it is worth it – is it worth squeezing that hard for that number of apples?"* If they accepted an offer (by exerting a small squeeze on the left hand-grip) then they had to squeeze to the required force and hold above this level for at least one second, within a five second response window. During the squeeze, online force feedback was shown as a red bar that indicated current force relative to the target line. If successful, they were 'rewarded' with the apples on offer, seeing the message *"xxx apples gathered"* as well as a cumulative tally of apples gathered on the current block *("total apples in basket: xxx")*. If unsuccessful the message displayed was *"0 apples gathered"*. Conversely, if participants rejected an offer (by exerting a small squeeze on the right-hand grip) they waited an equivalent time (to control for temporal discounting effects) before moving onto the next offer. Therefore, on each trial participants decided whether the value of an offer was worth engaging with, compared to doing nothing for the equivalent time. Before starting the experiment, participants practised each force level with each hand to familiarise themselves with the effort required, and completed a practice block in which they made decisions on the full range of options in the experiment.

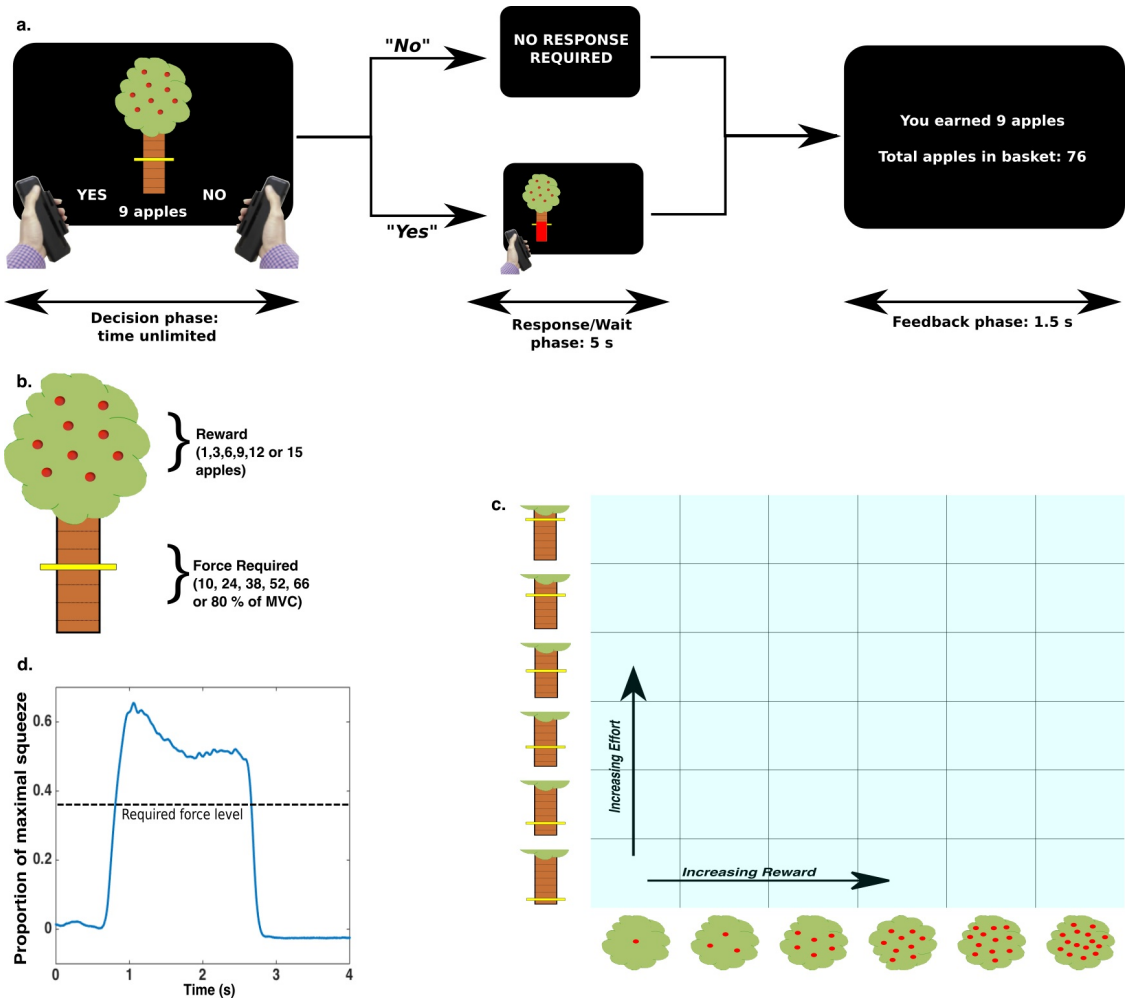


Figure 2-1. Effort-based decision making paradigm

On a trial-by-trial basis participants were presented with offers of a certain amount of reward (apples on an apple tree, with each apple worth 1p) in return for a level of physical effort (ranging between 10% and 80% of a subjects' previously-determined maximal voluntary contraction – **a & b**). They were instructed to weigh up each offer, deciding "whether it was worth it". If they accepted an offer (by squeezing the left-hand grip) the tree moved to the left or right of the screen, indicating which hand they had to perform the force squeeze with. They had a 5 second window within which to achieve the required force level. If they rejected the offer (by squeezing the right-hand grip) they waited the same 5 second period. After a feedback phase they then moved onto the next trial. After a practice session, participants worked through 180 trials, which evenly sampled the 6 x 6 'decision space' over 5 blocks (**c**). Example force trace from a single trial (**d**).

2.3.5.1 Rationale for specific experimental design choices

A number of features were included to reduce potential effects of fatigue during the task. Participants were only required to squeeze on 75% of accepted trials. Subjects were instructed to make each decision *"as if they would have to squeeze if they accepted the offer"* but were aware that on 25% of trials (pseudo-randomly distributed throughout the experiment) they would not have to squeeze. On these trials, they waited the equivalent time as if they had rejected the offer. Both hands were used for physical responses. The required response side was randomised and signalled on each trial *after* an offer was accepted, by the cartoon apple tree moving from the centre position to the left (left hand) or right (right hand) side of the screen. Finally, participants were allowed to rest between each block of 36 trials until they felt ready to continue (generally 30 – 120 seconds).

A potential criticism of the animal studies on which the design of this experiment is based (e.g. Walton *et al.*, 2002; Hauber and Sommer, 2009) is they do not explicitly control for temporal discounting – the observation that future rewards have a lower subjective value than immediate rewards (Frost and McNaughton, 2017). This could potentially devalue high effort options (which in rodent tasks may take longer to complete.) To avoid this confounder, the length of each trial was fixed, irrespective of a participant's choice. Put another way, *their choice on the current trial (accept/reject) did not influence the time until the next trial began, nor the number of future trials that were available to them.*

In this task the 6x6 decision space matrix was sampled evenly for each patient. Two key advantages of this approach were:

1) Raw data (choice, force metrics, decision time) was directly comparable between subjects, and could be analysed using linear or non-linear approaches
2) Conceptually, because the experiment was framed in the same way for all participants any differences observed between groups could be more easily related to everyday behaviour.

Previous versions of this task included a staircase design for presentation of effort/reward combinations (Bonnelle et al., 2015; Chong et al., 2015). This feature, in

which subsequent stimuli are determined by a participant's prior choices – usually to determine a stimulus which evokes a 50% response rate – has been extensively used in perceptual decision making paradigms, for example to determine visual perception thresholds (e.g. Mostert *et al.*, 2016). However, these perceptual paradigms vary presentation stimuli in a fine-grained way, something that was not possible using only 6 levels of reward and effort. Furthermore, observations of participants completing the staircase version of the task suggested their initial choices were quite influential as to which region of decision space (the reward * effort combination matrix) most offers were made from. This meant that over the course of the 180 trials, individual subjects often had very different options presented to them, and regions of the available decision space were often significantly under-sampled. The staircase procedure also constrained the analysis options to model-based strategies. Therefore, I elected to discard the staircase design, and instead evenly sampled decision space across the course of the experiment.

Because apathy manifests as a change in behaviour in *everyday life*, the chosen decision space matrix was intended to be as ecologically valid as possible (within the confines of the experimental task). The choice of effort levels ranging from 10% to 80% of an individual's MVC reflected variance in physical costs in everyday decisions (for example getting up off the couch to make a cup of tea carries only a low physical cost for most people, in contrast to choosing to run for a bus or mow the lawns with a push-mower). Choosing an appropriate range of reward levels was less clear-cut, given a theoretical boundless upper-limit of reward, however the strong influence of framing effects on behavioural decisions (Tversky and Kahneman, 1981) would suggest the absolute values chosen here were less important. I therefore utilised the same range (from 1 apple to 15 apples) that had shown a significant effect of reward on choice in prior studies (Bonnelle et al., 2016; Chong et al., 2015).

Each apple gained was worth 1p and participants were explicitly told they would be paid based on the number of apples gathered. Compared to primary reinforcers/rewards that are generally used in animal studies (e.g. food for a hungry rodent Walton *et al.*, 2002), money is a secondary reinforcer. However previous work has demonstrated that in humans primary rewards induce comparable neural responses and are described by

similar discounting functions as secondary (monetary) rewards (Prevost et al., 2010), so I do not believe this distinction is important in this task.

I chose to fix the accept/reject response side for the experiment (i.e. an accept response was always signalled by a small squeeze with the left hand) to avoid confusion for the patients performing the task.

2.3.6 Pilot data confirming utility of task

Prior to commencing the CADASIL patient study, I piloted the task in a sample of young University of Oxford students (n=12, mean age = 27, recruited via Experimental Psychology participant lists) and healthy elderly controls (n=15, mean age = 69, recruited via a local database). This was to ensure the task ran smoothly, instructions were sensible and could be consistently administered, and that independent effects of reward and effort were demonstrable **Figure 2-2**.

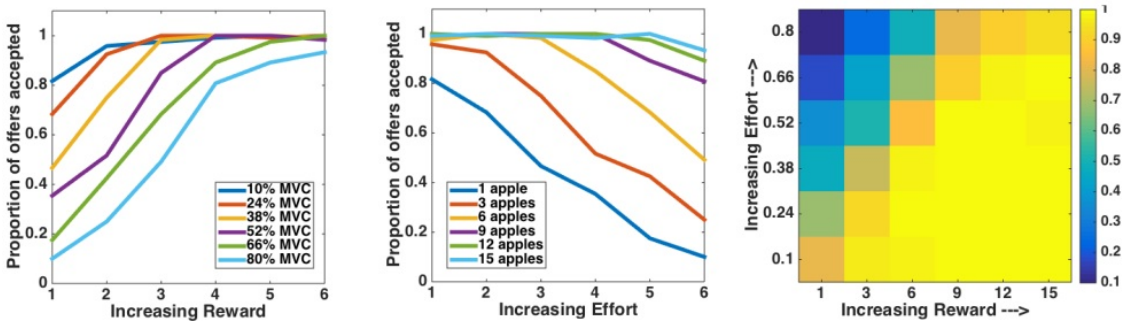


Figure 2-2. Pilot data from decision making paradigm

Independent effects of Effort and Reward on Choice are demonstrated in a cohort including young (n=12) and elderly (n=12) healthy participants. As number of apples offered increased, the mean proportion of offers accepted increased, for each effort level (**left**). Similarly, as required physical effort increased, the mean proportion of offers accepted decreased, for each reward level (**middle**). These results can be visualised by superimposing the proportion of offers accepted for each effort/reward combination onto the sampled decision space (**right**).

2.3.7 Analysis methods

Basic task measures, including the overall proportion of offers accepted, mean decision time and force metrics were analysed using either a standard one-way ANOVA (when including the control group) or unpaired t-tests for comparisons between the apathetic and non-apathetic CADASIL groups.

Choice data (the primary outcome of interest) was analysed in two separate ways. Firstly using a RM-ANOVA, with proportion of offers accepted for each of the 36 conditions as the dependent variable, reward and effort as within subject predictor variables and apathy a between subjects predictor variable. The dependent variable was arcsine transformed because it did not meet assumptions of linearity. A Greenhouse-Geisser correction was applied because assumptions of sphericity were not met (Mauchly's test: $\varepsilon = 0.317$, $p<001$). Residuals were examined following the analysis to ensure an approximately normal distribution.

Secondly, using a computational model of choice. Candidate models were selected based on prior decision making literature (Chong et al., 2017; Prevost et al., 2010) and intuition about how effort would affect the value of reward. I tested four general categories of model – Linear, Quadratic, Exponential and Hyperbolic effort discounting of reward (**Figure 2-3**). Each model ascribed a particular subjective value to each reward/effort combination, which varied depending on the parameters associated with reward and effort (fitted for each subject separately). A softmax function was used to transform this value to a number between 0 and 1 – the estimated probability of acceptance. Thus, for each subject and for each model, parameters for reward and effort as well as an intercept were estimated using the function *fminsearch* (Matlab, Mathworks, USA), such that the difference between a subject's actual accept/reject choices and the model estimates for each trial (log likelihood) were minimised. Model fits were compared using the Bayesian information criterion (BIC) and visual inspection of the individual and group average fits to the raw data.

The winning model was a non-linear exponential effort discounting model, which closely approximated both individual and group average choices **Figure 2-3**.

$$Value = \alpha Reward * e^{-\beta Effort} + k$$

Here α estimated the degree that reward (discounted by effort) increased the value of an offer, β estimated the degree that effort reduced the value of an offer, and k the baseline tendency to accept an offer. It should be noted, however, that this reward term does not dissociate reward completely from effort; rather it estimates the extent that *integrated reward and (discounted) effort* increase the value of an offer. If effort required (or indeed the effort parameter estimate) is zero, then the value of the offer is simply the reward * α (plus the intercept), whereas if reward is zero value is simply the subject's intercept. This captures the intuition that actions (effort exertion) are intrinsically linked to the rewarding outcomes they lead to. β and k parameter estimates, and $\log(\alpha)$ parameter estimate were normally distributed and therefore compared using unpaired t-tests.

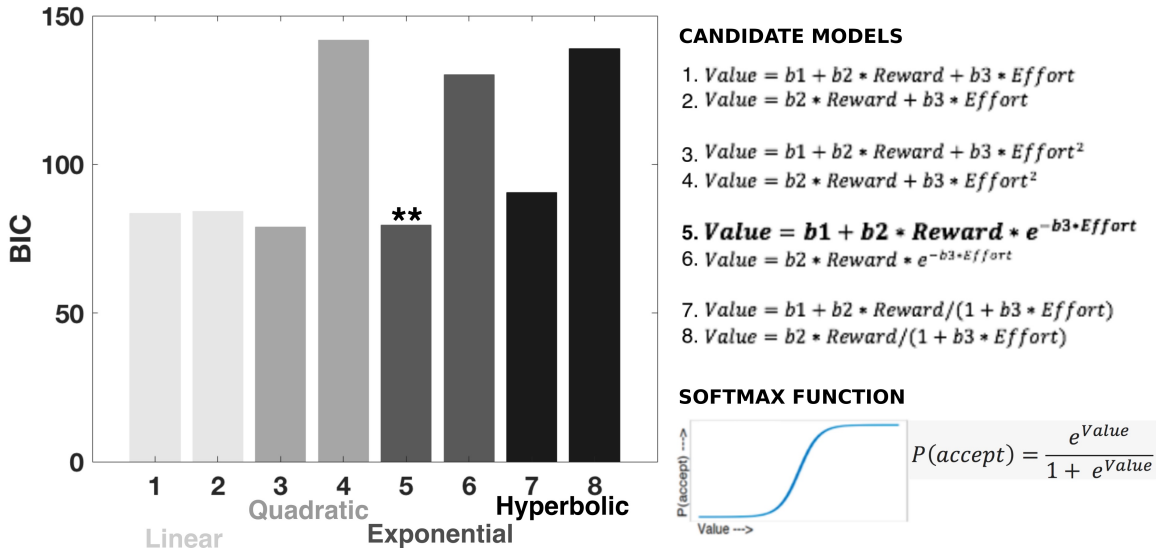


Figure 2-3. Model comparison for analysis of decision making choice data.

Candidate models were compared using median BIC value and visual inspection of model fits. The softmax function computed the probability of accepting an offer given its value. Model 5 was the winning model.

Measure	Control (N=19)	CADASIL (N=19)	p-value	CADASIL No Apathy (N=8)	CADASIL Apathy (N=11)	p-value
Age	54.5±11.2	54.3±10.3	0.96	55.8±11.1	53.3±10.1	0.62
Gender (F/M)	12/7	13/6	0.73	6/2	7/4	0.6
Apathy (LARS)	-28±3.6	-20±11.8	**0.007**	-29±3.5	-13.5±11.4	**0.0018**
Apathy (AES)	30.8±10.3	34.6±10.4	0.27	26.9±5.7	40.2±9.6	**0.0028**
GDS-total@	1±1.8	5.7±5.0	**<0.0001**	2.1±2.5	8.5±4.6	**0.003**
GDS-apathy	0.5±0.9	1.2±1.1	**0.04**	0.25±.046	1.9±0.87	**<0.0001**
GDS-depression	0.7±1.4	4.5±4.2	**<0.0001**	1.9±2.1	6.6±4.3	**0.012**
Fatigue@	29±10.8	27.6±15.5	0.77	16.4±5.8	36.3±15.2	**0.0057**
Quality of life - CANTRIL	8.1±1.6	6.6±2.2	**0.017**	8±0.9	5.5±2.3	**0.010**
Quality of life – WHO5	N/A	13.8±6.1	N/A	18.1±3.5	10.6±5.7	**0.0005**
ACE	96.6±2.4	92.3±5.3	**0.003**	94.9±2.4	90.3±6.1	0.064
Digit Span		6.1±0.8		6.1±0.8	6±0.8	0.74
Design Fluency	30.7±6.6	25.4±9.3	0.053	28.6±5.4	23±11.0	0.20
TMT – A@	N/A	30±15.7	N/A	22.8±8.0	35.8±18.2	0.08
TMT - B	N/A	86.7±54.3	N/A	65±27.1	104.1±65.1	0.13
TMT – B-A	N/A	56.7±41.4	N/A	42.3±25.2	68.3±49	0.19
NIHSS	N/A	0.05±0.2	N/A	0	0.09±0.3	0.41

Table 2-1. Demographics

^ Chi-square test

@ FSS data was missing for 3 patients; GDS and TMT data missing for 1 patient

2.4 Results

2.4.1 Apathy status

11 out of 19 patients were classified as apathetic. Results on the LARS and AES scales were highly correlated (r_{19}=0.73, p = 0.0004).

2.4.2 Demographics

Demographic measures are summarised in **Table 2-1**. In this sample, the presence of apathy was associated with greater depressive symptoms, higher fatigue levels and reduced quality of life on two distinct measures. Impairment on screening cognitive tasks, including the trail making task, digit span and design fluency was not significantly different between apathetic and non-apathetic patients, although performance on the ACE-III did trend to being lower in the apathy group. There were no significant differences in age or gender between the two CADASIL groups, or between CADASIL and control participants.

2.4.3 Global offer acceptance is reduced in apathetic patients

I first assessed the effect of clinical apathy on raw response rate (the proportion of offers accepted across the experiment). There was a significant main effect of group ($F(2,37) = 5.01$, p=0.012, **Figure 2-4a**). This was driven by CADASIL patients with apathy accepting significantly fewer offers than those without apathy (mean difference = 0.14, t_{17}=2.5, p=0.017) and healthy controls (mean difference = 0.14, t_{17}=3.0, p=0.005). There was no significant difference in global offer acceptance between non-apathetic CADASIL patients and healthy controls (mean difference = 0.005, t_{17}=0.1, p=0.93). Additionally, this global metric correlated significantly with the action initiation subscale of the LARS (r=0.64, n=19, p=0.003; **Figure 2-4c**).

2.4.4 Apathy is associated with reduced responding to low reward offers

To investigate the factors driving reduced offer acceptance in the apathetic population I used a repeated-measures ANOVA to analyse how the proportional acceptance rate in each cell of the sampled 6x6 decision space varied with reward, effort and apathy. The difference in responding was not global but rather varied with reward, but crucially not

with effort. There was a significant 2-way interaction between apathy and reward, but not between apathy and effort (**Figure 2-4d-f).**

Reward * Apathy; F(1.7,29.4)=4.3, p=0.028
Effort * Apathy; F(1.6,26.9)=0.40, p=0.63

That is, apathetic patients rejected significantly more offers when reward was low, but showed no difference compared to non-apathetic patients at high reward levels, irrespective of what the effort costs were. There were also significant main effects of apathy ($F(1,17)=5.0$, $p=0.038$), reward ($F(1.7,29.4)=38.4$, $p<0.001$) and effort ($F(1.6,26.9)=21.7$, $p<0.001$), and a 2-way interaction between reward and effort ($F(5.9,100.2)=3.6$, $p=0.003$). There was no 3-way interaction between apathy, reward and effort ($F(5.9,100.2)=1.3$, $p=0.25$).

2.4.5 Reduced incentivisation by rewards characterises apathy in CADASIL

Next I compared the parameter estimates for reward, effort and intercept obtained from the computational model of choice fitted to each participant's decisions (**Figure 5a)**. Modelled data very closely approximated raw choice data, both for each CADASIL patient (**Figure 5b**) and for group average choice proportions (**Figure 5c**). The *reward sensitivity* parameter estimate – which quantified the degree that the rewarding outcome of the action increased the value of an offer – was significantly reduced in apathetic CADASIL patients compared to the non-apathetic patients (Mean Difference ($\log(PE_{rew})$) = 1.67, $t_{17}=3.32$, $p=0.004$). In contrast, there was no significant difference between apathy and no apathy patients for the *effort sensitivity* parameter estimate (the degree that effort reduced the value of an offer – MD (PE_{eff}) = 0.47, t_{17} = 0.50, $p=0.62$) or for the *intercept* (the baseline tendency to accept an offer – MD (PE_{int}) = 0.84, t_{17} = 0.50, $p=0.63$).

Therefore, analysis using both raw choice proportions and a computational model demonstrated that the reduced responding associated with apathy in CADASIL was driven by reduced incentivisation by rewards, rather than hypersensitivity to the effort costs of actions.

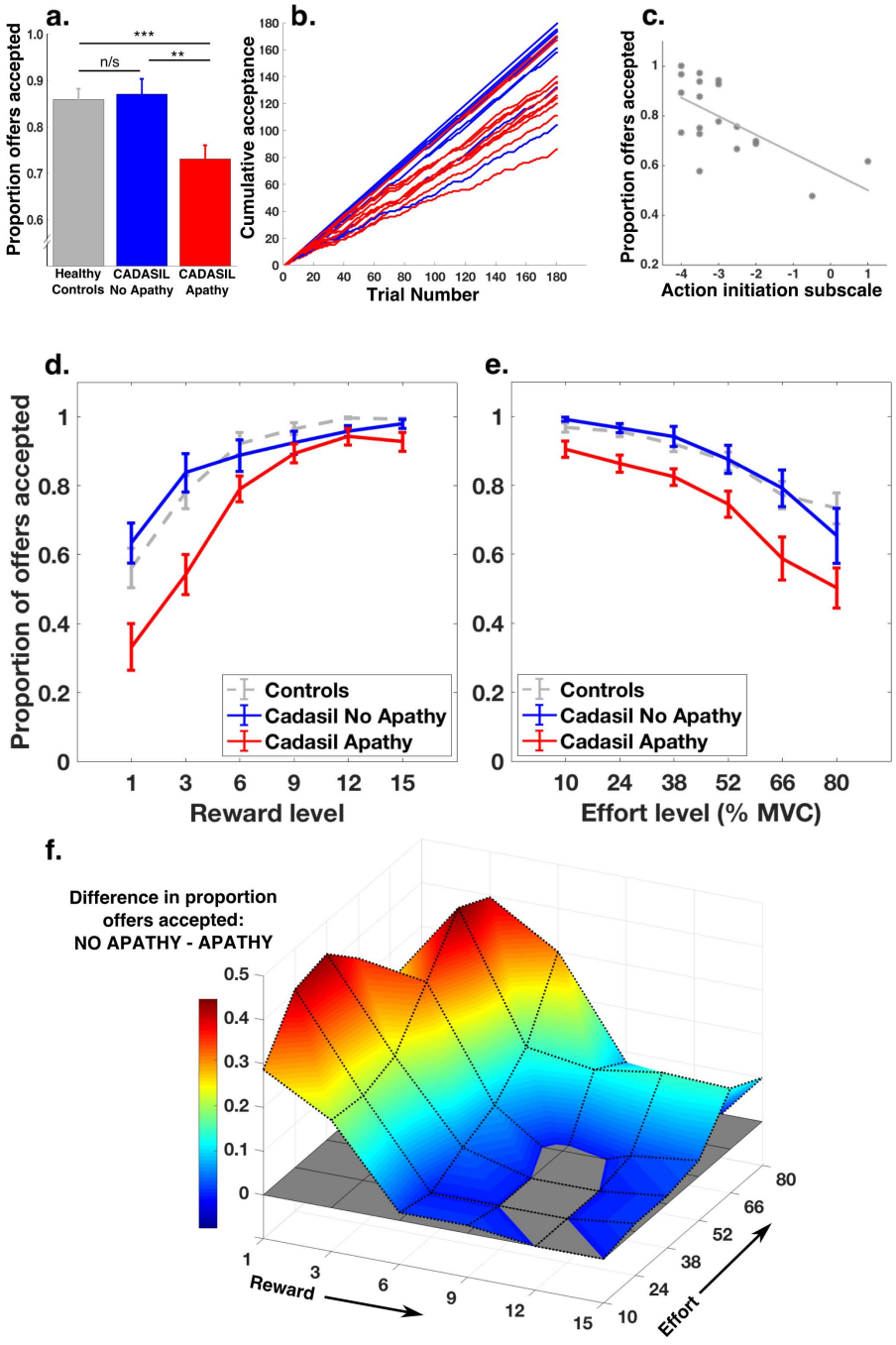


Figure 2-4. Altered effort-based decision making in CADASIL apathy

(a & b) Apathetic patients accepted significantly fewer offers than non-apathetic patients or healthy controls. **(c)** The proportion of offers accepted was significantly correlated with the action initiation subscale of the Lille apathy rating scale. **(d)** There was a significant apathy * reward interaction on offer acceptance. This plot shows the proportion of offers accepted as reward increases (collapsed across effort). Apathetic patients accepted fewer offers when rewarding outcomes were low, but performed the same as non-apathetic patients when rewards were high. **(e)** In contrast there was no apathy * effort interaction. This plot shows offer acceptance as effort level increases (collapsed across reward). **(f)** The difference in offers accepted between no apathy and apathy group occurred in a distinct region of decision space – where offers were for low rewards, irrespective of effort required. *Plots **a, d** & **e** show mean ± SE.*

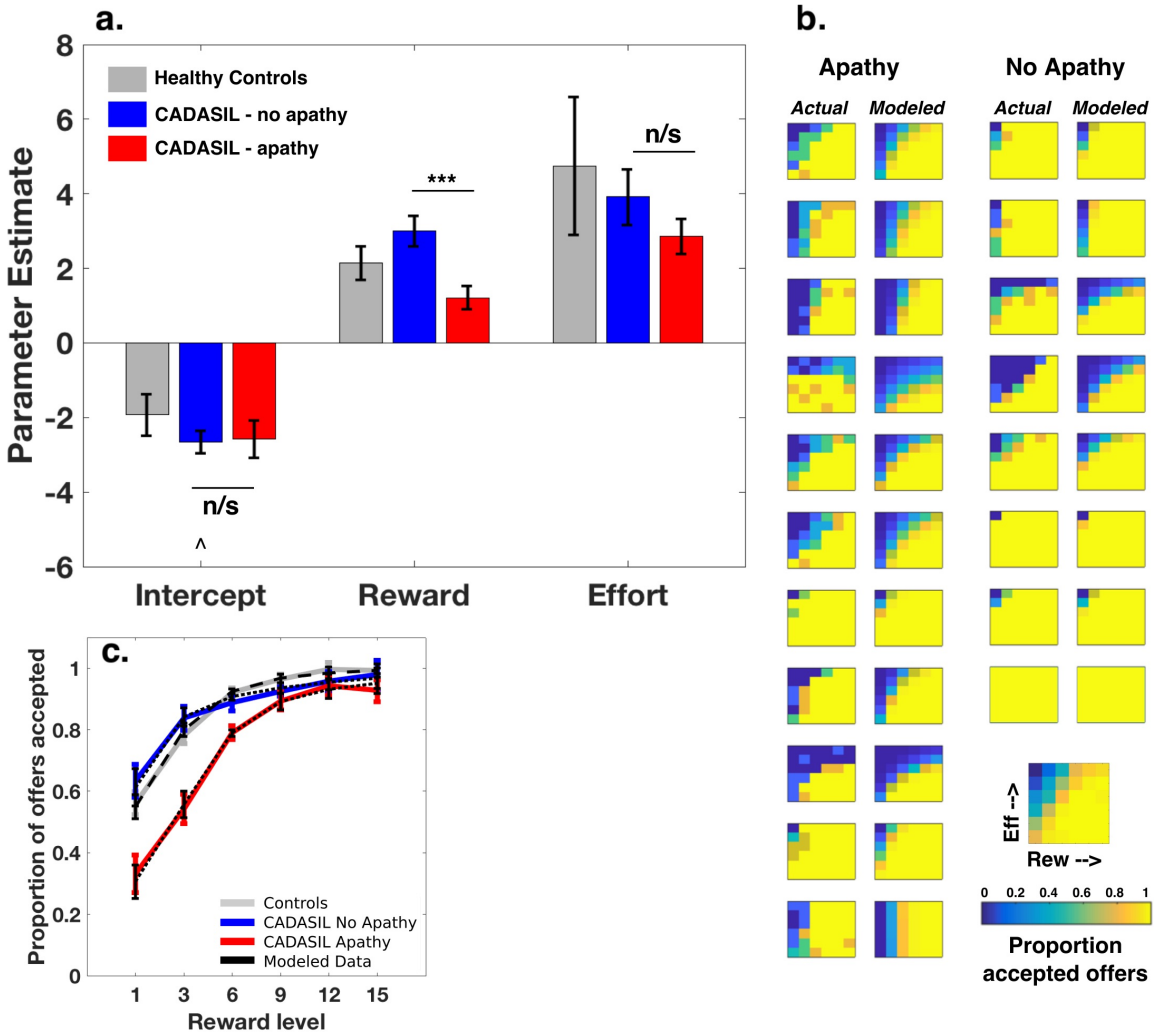


Figure 2-5. Apathy in CADASIL is characterised by reduced incentivisation by rewards

(a) The reward parameter (α) was significantly lower in apathetic compared to non-apathetic patients, whilst neither the effort parameter (β) nor intercept (k) were significantly different. **(b)** Actual and modeled choice proportions for each apathetic (left columns) and non-apathetic (right columns) CADASIL patient. **(c)** Group level choice proportions with increasing reward, with model fits superimposed (black dotted lines).

One patient (no apathy) accepted all offers and had an outlying (positive) intercept. For clarity this participant's parameter estimates were not plotted, however they were included in the analysis (inclusion or exclusion did not change any reported results).

2.4.6 Decision time

The time each participant took to accept or reject an offer varied significantly by group, with both controls and non-apathetic CADASIL patients significantly faster than apathetic patients (Main effect of group: $F(2,33)=5.8$, $p=0.007$; mean difference CADASIL-Apathy vs Controls = 1.1s, $t_{28}=3.39$, $p=0.002$; mean difference CADASIL-Apathy vs CADASIL-No Apathy = 0.85s, $t_{17}=2.04$, $p=0.05$; mean difference

CADASIL-No Apathy vs Controls = 0.27s, t_{25}=0.70, p=0.49; RM-ANOVA. There was also a main effect of decision type – "*yes*" decisions were significantly faster than "*no*" decisions: F(1,33)=10.66, p=0.003. This decision-type effect was strong in both the control (MD=0.4s, t_{17}=7.4, p<0.0001) and non-apathetic patient groups (MD=0.4s, t_6=4.5, p=0.004), but not present within the apathy group (MD=0.01s, t_{10}=0.04, p=0.96). However the group * decision type interaction did not reach the threshold for statistical significance, F(2,33)=2.71, p=0.081 (**Figure 2-6**)

Decision time also provides a metric to assess task engagement. A basic prediction is that regions of decision space where subjects are more variable in their choice (and therefore more uncertain) should have longer decision times than "easier" choices (for example regions of decision space which are always accepted or rejected). I split choices into 2 categories – ***easy*** (accepted < 25% or > 75%) and ***hard*** (accepted 25-75%), to determine if indeed this prediction held in all groups. There was a main effect of decision difficulty, F(1,29)=44.76, p < 0.001 (**Figure 2-6**). This effect was present in both CADASIL groups, however was not statistically significant in the control group, giving rise to a 2-way interaction between decision difficulty and group. RM-ANOVA and paired t-test results were: Group * Difficulty interaction: F(2,29)=9.05, p=0.001. Mean difference (Hard – Easy) Controls: 0.1s, t_{15}=1.43, p=0.17; M.D. CADASIL No Apathy: 0.74s, t_5= 3.93, p=0.01; M.D. CADASIL Apathy: 0.41s, t_9=4.17, p=0.002.

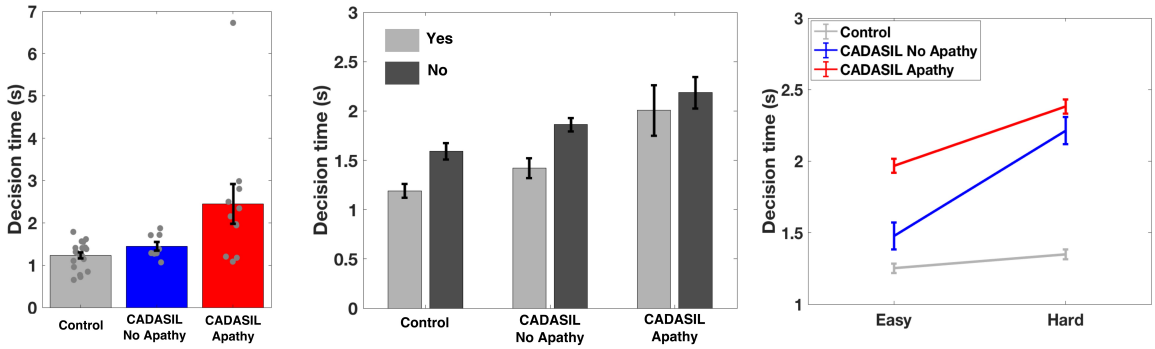


Figure 2-6. Decision time metrics

Apathetic patients were slower to decide whether to accept or reject an offer than both non-apathetic patients and healthy controls (who did not significantly differ (**left**). Both controls and non-apathetic patients accepted decisions faster than they rejected them, but this effect was not present in apathetic patients (**centre**). Decision time varied as a function of choice difficulty (probability of acceptance). That is, patients (although not controls) spent significantly longer on "hard" decisions (probability of acceptance: 25% – 75%), than "easy" decisions (probability of acceptance: <25% or >75%, **right**).

2.4.7 Control Analyses

Participants in both CADASIL groups and the control group parametrically modulated their force output to task requirements (main effect of force level: $F(1.8,60.2)=517.5$, $p<0.001$ **Figure 2-7 top left panel**). Additionally, there was no effect of group-type on force modulation, meaning in particular that apathetic and non-apathetic patients both adjusted their force output to the same degree (force required * group interaction $F(3.5,60.2)=1.4$, $p=0.26$). Participants on average achieved required force levels >95% of the time: mean success rate for controls, CADASIL-No Apathy and CADASIL-Apathy 98.6%, 96.2% and 96.7% respectively (**Figure 2-7 top right panel**). There was no significant difference in performance between apathetic and non-apathetic CADASIL patients ($t_{17}=0.32$, $p=0.75$), although there was a main effect of group on success rate, driven by controls achieving required force levels at a higher rate than both apathetic and non-apathetic CADASIL patients: $F(2,37)=3.7$, $p=0.035$; Control vs CADASIL-No Apathy $t_{25}=2.4$, $p=0.02$; Control vs CADASIL-Apathy $t_{28}=2.7$, $p=0.01$). Participants' choices did not systematically change across the course of the experiment, with no effect of block number on acceptance rate in apathetic ($F(4,179)=0.15$, $p=0.96$), non-apathetic ($F(4,179)=0.81$, $p=0.52$) or control subjects ($F(4,179)=0.41$, $p=0.8$; **Figure 2-7 bottom panels**).

2.4.8 Depression and apathy

In this population of 19 CADASIL patients, depression and apathy were strongly correlated ($\rho_{spearman} = 0.61$, $n=18$, $p=0.008$). It was therefore not possible to effectively examine the effects of depression on choice, independent of apathy (for example a median split of group based on the GDS depression subscale classified only three apathetic patients in the 'low depression' group, and two non-apathetic patients in the 'high depression' group). Nevertheless, using the same RM-ANOVA setup as above – but including a between subjects effect of depression (low vs high) instead of apathy – did *not* reveal a significant main effect of depression on choice: $F(1,17)=1.7$, $p=0.21$. Additionally, there were no significant two-way interactions (depression * reward: $F(1.6,26.5)=1.1$, $p=0.33$; depression * effort $F(1.6,26.6)=0.12$, $p=0.84$) or a significant three-way interaction (depression * reward * effort $F(5.5,94)=1.9$, $p=0.09$).

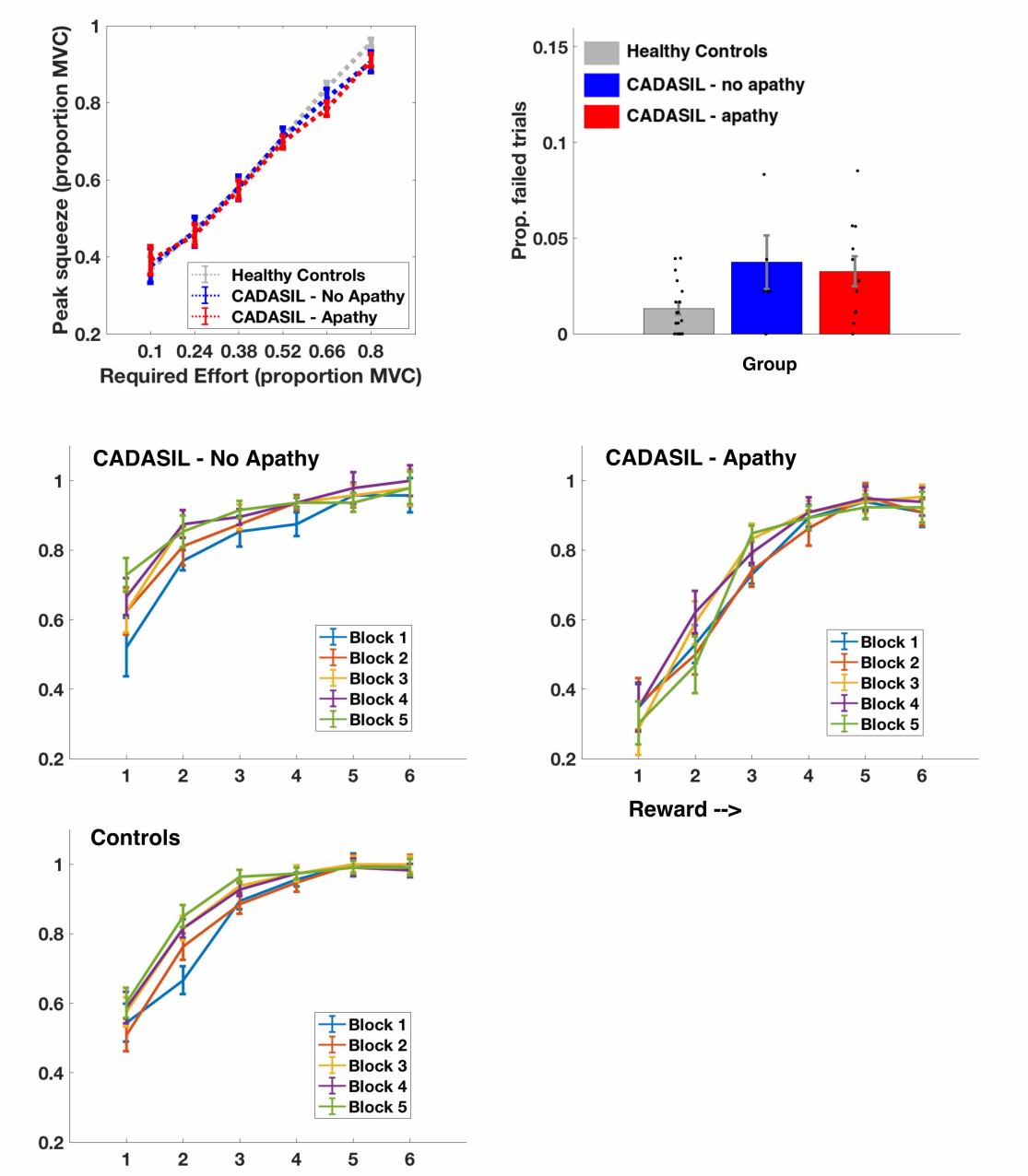


Figure 2-7. Control Analyses

Participants in all groups parametrically modulated their grip force to trial requirements (top left panel). They achieved required force levels >95% of the time, with no difference in success rate between apathetic and non-apathetic patients (top right panel). Participant choices did not change as a function of block number in any group (bottom panels).

2.5 Discussion

This study demonstrates that effort-based decision making is altered in apathetic CADASIL patients, leading them to reject significantly more offers of reward for exerting effort. This reduced acceptance is not general, but manifests in a specific region of the sampled decision space: those offers in which rewards are low. Furthermore, patients with CADASIL who were not apathetic performed the same as age and gender-matched healthy controls demonstrating that the behavioural changes were specific to apathy, rather than occurring as a more general part of the CADASIL disease process. The lack of significant differences on cognitive measures as well as the specific rather than general changes in decision making associated with apathy suggest the study observations are unlikely to be explained by a confounding cognitive problem. Further strengthening this point is the fact that the apathetic group modulated their force production to force requirements, and showed expected variation in decision time with choice difficulty. Additionally, the study protocol controlled for other confounders such as fatigue and temporal discounting, while, despite the higher rates of depressive symptoms in the apathetic group, the same behavioural effects were not present when using dysphoria instead of apathy to split the patients.

Computational modelling confirmed that the reduced acceptance of low reward offers by apathetic CADASIL patients was driven by reduced incentivisation by the rewarding outcomes of actions, rather than increased sensitivity to the action costs themselves. Put another way, apathetic patients were prepared to exert as much effort as non-apathetic patients – even at high effort levels – *if the rewarding outcome was high enough*. This finding of reduced incentivisation by reward in apathetic patients has support in the literature from studies that have demonstrated impaired incentive processing associated with apathy in other conditions, particularly Parkinson's disease. Apathy in Parkinson's disease has been associated with reduced autonomic (Muhammed et al., 2016; Schmidt et al., 2008) and neural (Lawrence et al., 2011) responses to reward. PD patients with apathy also show reduced electrophysiological responses (feedback related negativity) to rewarding and aversive outcomes, suggesting an impairment in underlying incentive processing (Martinez-Horta et al., 2014b). These reward related signals are likely crucial for motivating behaviour

towards a goal, overcoming the costs of action as an individual decides whether or not to act (Holroyd and Yeung, 2012; Rushworth et al., 2012; Salamone et al., 2016). However, this previous body of work has not assessed the relationship between decisions to act and markers of reward sensitivity, as performed in the current study.

Although this experiment demonstrates a failure of reward to incentivise choice – rather than effort hypersensitivity – in apathetic patients, we cannot deduce which specific components of effort-based decision making are changed in the apathetic state. The result could theoretically arise either from diminished valuation of rewarding outcomes (for example due to pathology within medial orbitofrontal cortex or its connections (Rushworth et al., 2012), or from reduced efficiency of integration of the reward value signal with effort costs, a process more closely associated with dorsal anterior cingulate cortex (Hauser et al., 2017; Kennerley et al., 2009; Rushworth et al., 2012). Interestingly, disruption of white matter connections underlying both of these brain regions has been associated with apathy in SVD (Hollocks et al., 2015). The behaviour of the apathetic patients studied here is also consistent with the basic neuroscientific work on which the paradigm was based. Although medial frontal cortex lesions in rodents biased them away from choosing high effort, high reward options (Hauber and Sommer, 2009; Walton et al., 2002), a further experimental manipulation in which the *relative difference in reward* between low and high effort options increased (equivalent to the high reward conditions in the current paradigm), restored the preference in lesioned animals to accept the high effort option (Walton et al., 2002).

To my knowledge, this is the first study to demonstrate that effort-based decision making is altered in clinically apathetic patients with CADASIL, and with SVD more generally. The findings in this study are consistent with earlier work examining effort-based decision making in schizophrenic patients (Hartmann et al., 2015). The authors found that apathy, but not diminished facial expression (both important negative symptoms of schizophrenia) was associated with less willingness to exert effort for reward (money). However, they did not dissociate the effects of reward and effort on choice. There are no reasons to suspect the broad findings of this study will not be generalizable to apathy occurring in other conditions, particularly given the overlap in implicated brain regions and commonality of the clinical phenotype (Le Heron et al.,

2017). In Chapter Four I present the results of a similar study in patients with Parkinson's disease, but future work should also focus on other neurological conditions in which apathy commonly manifests.

Although both raw acceptance rates and the reward parameter correlated significantly with the overall LARS, this was mainly driven by the *action initiation* (AI) subscale. This finding is consistent with previous work, where this subscale correlated with imaging measures of connectivity between anterior cingulate cortex and the supplementary motor area in healthy individuals (Bonnelle et al., 2016), and with autonomic responses to reward in Parkinson's disease (Muhammed et al., 2016). Indeed, the questions that comprise the AI subscale emphasize a person's daily activities, and their need for prompting in doing daily tasks. These two factors are at the core of the conception of apathy as a disorder of goal directed behaviour (Levy and Dubois, 2006). They also require a decision to engage, something that is explicitly tested in this task. An open question is how the other questionnaire components of the LARS, and indeed other apathy measures, relate to underlying neurobiological mechanisms (Ang et al., 2017) and see **Chapter 7**.

An alternative approach to this question, however, is to understand the neurocognitive mechanisms of apathy – and other cognitive syndromes – based on knowledge of the normal functioning of implicated systems (Holroyd and Umemoto, 2016; Le Heron et al., 2017; Salamone et al., 2016). Here I have demonstrated apathy is associated with specific changes in one component of effort-based decision making – deciding whether or not to engage in an offer – but there are other aspects not examined in the current study. These include persistence towards a goal (Hamid et al., 2016; Holroyd and Yeung, 2012; Howe et al., 2013), learning from the outcomes of actions (Hauser et al., 2017; Holroyd and Umemoto, 2016; Scholl et al., 2015), and tracking background environmental reward information in order to compare the value of current actions with alternatives (Hayden et al., 2011). In the latter parts of this thesis, I investigate the role some of these other aspects of effort-based decision making may play in the apathetic syndrome.

Apathetic patients took longer to make both accept and reject decisions than non-apathetic patients and healthy controls. Interestingly in the study population non-task

related measures of processing time (Trail making task, design fluency) were not significantly different between apathetic and non-apathetic patients, suggesting this increased decision latency was specific to the decision process, rather than a more general phenomenon. Future work could explore this observation further, as one possible – although speculative – explanation would be that apathetic patients show longer decision latencies due to inefficient integration of reward and effort information to drive choice.

Although healthy controls and non-apathetic patients accepted decisions faster than the rejected them, this effect was not observed in the apathetic group, who showed no decision-type effects. This could be interpreted as a bias away from accepting offers. However, the computational model suggested that the intercept – effectively a person's baseline tendency to reject an offer – is not lower in apathetic patients, which would not be consistent with this hypothesis. It remains an open question, therefore, how the lack of decision-type (yes/no) effect relates to observed apathetic behaviour.

This study demonstrates that apathy in CADASIL is associated with altered effort-based decision making – driven by reduced incentivisation by the rewarding outcomes of actions, rather than the action costs themselves. More generally, these results suggest that in everyday life the core feature of clinical apathy – reduced goal directed behaviour – may manifest because patients no longer derive sufficient 'drive' from the outcomes of options in their environment to activate behaviour. As in some previous studies, apathy in this CADASIL group was associated with a significantly lower quality of life, underlining the importance of establishing a mechanistic understanding of this syndrome (Hollocks et al., 2015; Mayo et al., 2009; Reyes et al., 2009).

The results presented here demonstrate the utility of framing apathy as a disorder of decision making – a conceptualisation that may well apply to other neurological conditions as well. It also identifies a concrete goal of potential therapeutic interventions – to increase the incentivising effects of reward – an issue explored in further detail in **Chapter 4**. The computational model outputs an estimate of each person's reward incentivisation, the axis within which apathetic changes manifest in this study. In the next chapter I investigate whether this marker is related to autonomic

markers of incentivisation by reward, and anatomical changes within regions that underpin the process of integrating rewarding outcomes with their action costs.

3 Physiological and anatomical correlates of apathy in CADASIL

3.1 Chapter Summary

In this chapter I investigate the physiological and anatomical correlates of apathy in CADASIL using an eye movement task to measure pupillary responses to reward, and an analysis of white matter tract integrity using diffusion MRI. The relationship between these metrics and the behavioural measure of reward incentivisation derived in the previous chapter are also examined. The results demonstrate that apathetic patients have blunted autonomic responses to rewards, mirroring the behavioural reward insensitivity described in the last chapter. Furthermore fractional anisotropy values in the apathy group were reduced compared to non-apathetic CADASIL patients within white matter tracts linking regions considered to be crucial for effort-based decision making, including anterior cingulum, orbitofrontal white matter and the anterior limb of the internal capsule. The behavioural estimate of reward incentivisation correlated with both physiologically measured (pupil) reward sensitivity and FA values within these identified tracts. Together with the previous chapter, these experiments provide behavioural, physiological and anatomical evidence of altered effort-based decision making in CADASIL patients with apathy, driven by reduced incentivisation by the rewarding outcomes of actions.

3.2 Introduction

The cognitive mechanisms that underlie apathy remain poorly understood despite increasing recognition of its prevalence and impact on patients and their families. The pathognomonic feature of apathy is a reduction in goal directed behaviour, and previous frameworks have guided mechanistic research by highlighting the link between aspects of normal goal directed behaviour and the apathetic syndrome (Levy and Dubois, 2006; Marin, 1991). Based on a synthesis of the neuroimaging and basic neuroscience literature, a recent framework identified a central aspect of goal directed

behaviour – effort-based decision making – as a particularly promising model for understanding the mechanisms of apathy (Le Heron et al., 2017).

A core feature of this cognitive process is the integration of reward and effort information to guide choice about actions – or sequences of actions – towards potential goals. In the previous chapter I demonstrated that apathy in CADASIL – a genetic condition characterised by extensive cerebral SVD (Chabriat et al., 2009) – was associated with disrupted effort-based decision making. This change was driven by reduced incentivisation by the rewarding outcomes of actions rather than hypersensitivity to the action costs themselves. Disrupted physiological responses to incentives have also been associated with apathy in Parkinson's disease (Lawrence et al., 2011; Martinez-Horta et al., 2014b). However no mechanistic studies have been carried out in SVD – whether sporadic or genetic – and it is unclear whether the results from patients with Parkinson's disease would generalize to a very different clinical group such as patients with SVD. In addition, to the best of my knowledge, no study in any neurological condition has examined behavioural, physiological and anatomical components of effort-based decision making in the same group of apathetic patients, limiting the strength of conclusions that can be drawn from the existing body of work. For example, Muhammed and colleagues recently demonstrated blunted pupillary responses to rewards in apathetic patients with Parkinson's disease (Muhammed et al., 2016). The noradrenergic system is considered to mediate preparation of effort (Varazzani et al., 2015), and thus pupillary dilatation in response to rewards might provide an autonomic marker of motivation (Chiew and Braver, 2014; Manohar and Husain, 2015). However, participants in the task used in Parkinson's disease were not required to make decisions about whether or not to work for these rewards, so the functional consequences of this blunted response remain unclear.

In addition to the lack of mechanistic studies of apathy in SVD, there is also a dearth of imaging studies compared to other neurodegenerative conditions, such as Parkinson's disease (Wen et al., 2016) or Alzheimer's disease (Theleritis et al., 2014). To date, there is only one report of the neural correlates of apathy in CADASIL (Jouvent et al., 2011), and, as far as I am aware, there is no previous report which has examined associations with specific changes in white matter tracts, despite this being the pathognomonic site of pathology in the disorder (Chabriat et al., 2009). Apathy in

sporadic SVD has also been associated with global burden of vascular disease, however these whole-brain measures do not allow for a mechanistic interpretation of underlying causes (Hollocks et al., 2015; Jonsson et al., 2010; Kim et al., 2013; Lavretsky et al., 2008). One recent study has examined the relationship between fractional anisotropy (FA – a measure of white matter tract integrity) and apathy in sporadic SVD (Hollocks et al., 2015). The authors found apathy was associated with reduced FA within the anterior cingulum, uncinate fasciculus and fornix. Importantly, these white matter tracts link the brain regions strongly implicated in the development of apathy in other conditions – regions in which the process of effort-based decision making is instantiated (Le Heron et al., 2017). However, as with other imaging studies, aside from the questionnaire measure used to define apathy no behavioural measures of effort-based decision making were available in these patients.

One barrier to performing specialised imaging analyses in the CADASIL population is the extensive white matter lesions that characterise the condition. These can interfere with pre-processing of raw images and compromise registration of patients' scans to a common template, a crucial step in any group analysis (Sdika and Pelletier, 2009). However a tool for automated white matter lesion mapping has recently been developed and piloted in sporadic SVD patients (Griffanti et al., 2016). This provides an automated method to extract lesion information from images of CADASIL patients, and minimise the effects these lesions have on pre-processing steps by excluding them from registration steps.

In the previous chapter I computed an estimate for each patient of the degree that reward incentivised choice behaviour. Here I used this metric, along with group differences (apathy vs no apathy) to establish whether the reduced reward sensitivity demonstrated behaviourally in apathetic CADASIL patients (described in the previous chapter) is associated with underlying physiological and anatomical changes consistent with impaired reward processing.

Firstly I investigated whether apathy is associated with blunting of an autonomic marker of reward sensitivity – pupillary dilatation to reward – and whether this marker correlates with behavioural reward sensitivity. Secondly, I used a tract-based spatial statistics (TBSS) analysis of diffusion MR sequences to test the hypothesis that apathy

in CADASIL is associated with reduced FA within white matter tracts linking crucial regions for effort-based decision making. I also estimate total white matter lesion volume using the recently developed automated white matter segmentation technique BIANCA (brain intensity abnormality classification algorithm) (Griffanti et al., 2016).

The overarching aim of this chapter is to determine whether behavioural patterns of response in CADASIL apathy – reduced incentivisation by rewards – are linked to both physiological measures of reward sensitivity, and to changes within the neural regions that subserve these processes.

3.3 Experiment ONE: Blunted autonomic responses to reward in CADASIL apathy

3.3.1 Methods

Participants

The 19 CADASIL patients, along with the 19 age and gender matched healthy controls, who undertook the effort-based decision making task presented in Chapter TWO also undertook this experiment – usually on the same day as the decision making task. Data for one control was not usable due to difficulty with equipment. The demographic data for these subjects is presented in **Table 2-1**.

Experimental Paradigm

The eye tracking task used in this study has been described in detail in a previous publication, when it was used in a cohort of patients with Parkinson's disease (Muhammed et al., 2016). The task involved participants performing saccadic eye movements from a central fixation point to a peripheral target to earn monetary rewards (**Figure 3-1**). Three levels of reward were used: 0p, 10p and 50p. These values were the maximum amount that could be earnt on the current trial, and were conveyed to participants via an audio cue once they had maintained central fixation for 500ms. Then, following a period of 1400, 1500 or 1600ms, the fixation cue disappeared and concurrently a peripheral target cue appeared, randomised between left and right, at an

angle of 11°. This was the participant's cue to saccade as quickly as possible to the new target.

Participants were aware that the proportion of the maximal earnings they were paid depended on how quickly they reached the target. Although the absolute reward earned varied with this metric, the amount was dynamically adjusted for each participant via an adaptive exponential fall-off based on their average time on the preceding 20 trials. Therefore, difficulty level remained consistent across the experiment, accounting for potential confounding factors such as fatigue and baseline reaction time, whilst also ensuring equal rewards were earned by all participants. After reaching the cue, visual feedback about the amount earned on that trial was displayed within the target, as well as an audible bell sound if they earned more than 10p, and a cash register sound if they earned more than 30p. No sound was played for less than 10p earned. Participants performed five blocks of 54 trials each, with the three reward levels interleaved through each block. They were given a 5-min break between the first three and last two blocks. In total each participant completed 270 trials, with 90 trials for each of the three reward levels.

An infrared eye tracker (Eyelink 1000, SR Research) was used to monitor pupil diameter and eye position. Disc luminance was matched across all trials so as not to affect pupil dilation. Eye tracking was performed in a dimly lit room 60 cm in front of a 21" CRT (1024 × 768 pixels; 100 Hz refresh). Stimuli were presented on a Windows computer running Matlab (The MathWorks) and Psychophysics Toolbox. The frame-mounted infrared tracker monitored left eye position and sampled at 1 kHz. Eye movements were measured online by the Eyelink computer and transferred directly to the presentation computer to provide immediate feedback. Nine-point calibration was performed. Pupil dilation was calculated as a proportional change from average baseline pupil size measured in Eyelink units. Recordings were time locked to the reward cue onset and normalized using a 200 ms baseline subtraction for each trial. Pupil traces lost due to blinks were interpolated. A moving average smoothing window of 100 ms was applied to the final recordings.

Eye movement analysis was carried out using custom-made Matlab code. An eye movement was classified as a saccade if it was >2°, and the accepted landing area to

register completion of the saccade was 5° in radius from target centre. The first landing point within the target area was used to classify saccade completion. Reaction time was calculated from target onset to the time when a saccade was registered as complete, and peak saccadic velocity computed as maximum velocity recorded during the saccade.

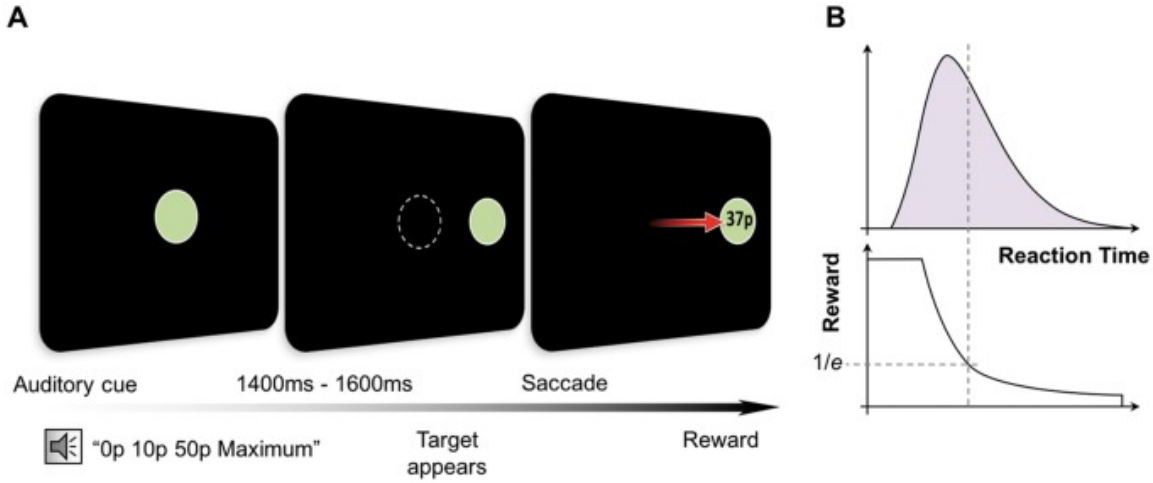


Figure 3-1. Eye tracking paradigm

(a) Participants fixated on a disc displayed on a desktop monitor linked to an infrared eye tracker. At the beginning of each trial participants heard an auditory cue ("0p/10p/50p maximum") informing them the maximal amount they could win on that trial. Following a delay of 1400-1600ms the central disc disappeared and concurrently a target disc appeared on one side, cueing a saccade to this location. Participants were rewarded with a proportion of the maximum amount available based on the time taken to reach the target**)**. **(b)** Although the absolute amount of reward varied with reaction time, this was dynamically adjusted according to the mean reaction time of the last 20 trials. Therefore, difficulty level was maintained across the experiment and overall participants received equal reward amounts.
Adapted from (Muhammed et al., 2016) *with permission*

Statistical Analysis

The eye tracking task data was analysed according to a previously published approach (Muhammed et al., 2016). Pupillometry analysis was performed using a one-way ANOVA to test for group differences in the variables of interest (CADASIL apathy, CADASIL no apathy and controls), and two-sided t tests for subsequent comparisons of average pupil responsiveness between groups, with significance level set at *p*-values of <0.05. Pearson correlations were used for parametric behavioural outcome comparisons. Time periods for averaging pupil responses were chosen based on past

work (Muhammed et al., 2016). Additionally, differences in pupillary reward sensitivity were analysed over time at each millisecond time point using multiple permutation testing (to account for multiple comparison bias).

3.3.2 Results

Pupillary response to reward

Apathetic CADASIL patients showed significantly blunted pupillary responses to reward. There was a significant main effect of group on the mean proportional pupil change between the 50p and 0p conditions ($F(2,34)=4.3$, $p=0.021$). This was driven by a reduced change in pupil size as reward increased in the apathy group, compared to the no apathy group (mean difference = 0.75 ± 0.29, $t_{17}=2.39$, $p=0.029$) and the healthy matched controls (md = 0.61 ± 0.24, $t_{27}=2.94$, $p=0.007$). There was no difference between non-apathetic CADASIL patients and controls (md = 0.14 ± 0.27, $t_{24}=0.49$, $p=0.63$). The differences in the apathetic group became significant approximately 1400ms following display of the reward stimulus (
Figure 3-2**a & b**). Importantly there was no significant difference in baseline pupil size between groups ($F(2,34)=0.68$, $p=0.51$), meaning the reduced response associated with apathy could not simply be explained by these patients having greater dilatation at the start of the experiment.

There was a significant correlation between the mean proportional change in pupil size (50p – 0p) and the reward parameter estimate derived from behaviour in the effort-based decision making task presented in the previous chapter ($R=0.45$, $N=36$, $p=0.006$) **Figure 3-2c.** Therefore a reduction in reward incentivisation on the decision making task was associated with reduced physiological markers of reward sensitivity, as measured by pupillary responses to reward, and both these metrics were significantly diminished in the apathy group.

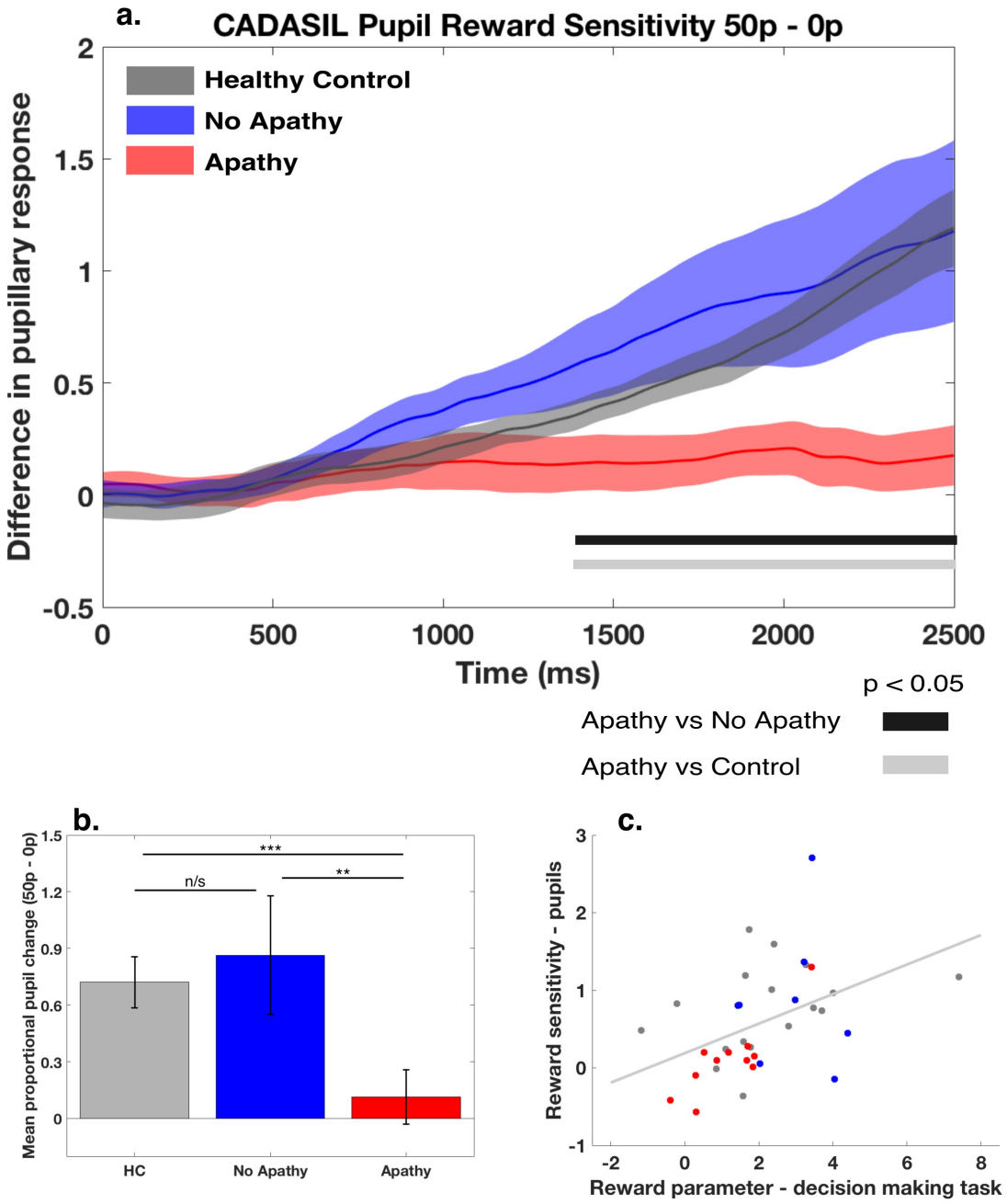


Figure 3-2. Blunted pupillary responses to reward in CADASIL Apathy

(a) Apathetic CADASIL patients had a significantly diminished pupillary response to increasing incentives compared to both non-apathetic patients and healthy controls. Reward sensitivity (indexed as the difference in pupil dilatation between the high and no reward conditions) is plotted at each time point for the 2500ms following reward stimulus presentation. **(b)** Mean reward sensitivity (time period 1400-2400ms) was significantly lower in the apathetic group compared to non-apathetic patients and controls. **(c)** Physiological reward sensitivity, as indexed pupillary response to reward, was significantly correlated with the reward parameter estimate from the effort-based decision making task; Red dots: CADASIL apathy; blue dots: CADASIL no apathy; grey dots: controls. *Mean ± SE shown in **a** & **b**.*

Saccadic velocity

There was no significant difference in peak saccadic velocity between apathetic and non-apathetic CADASIL patients or healthy controls: Group difference (RM-ANOVA): $F(2,34)=0.24$, $p=0.79$; Mean(No Apathy) = 545±25 degr/s; Mean(Apathy) = 523±21 degr/s, $p=0.58$. Therefore, although apathetic patients showed blunted pupillary responses to reward, their subsequent saccade to the rewarding target reached the same peak velocity as non-apathetic patients and controls **(Figure 3-3a).** There was a significant main effect of reward on velocity with participants reaching a higher peak saccadic velocity as reward level increased: mean 0p = 525 degr/s; mean 10p = 531 degr/s; mean 50p = 534 degr/s, $F(2,68)=6.8$, $p=0.002$. There was however no reward * group interaction, indicating this effect was present across all groups – $F(4,68)=1.43$, $p=0.24$. There was no correlation between reward sensitivity indexed by change in saccadic velocity (50p – 0p) and the reward parameter estimate from the decision making task ($R=0.074$, $N=36$, $p=0.678$) (**Figure 3-3b**). Reaction time (time to saccade to target following cue to move) did not differ as a function of apathy (Mean Difference (No Apathy vs Apathy) = 7ms, $t_{17}=0.41$, $p=0.69$), nor was there a significant group effect: $F(2,36) = 2.2$, $p=0.13$ (**Figure 3-3c)**.

Therefore, although apathetic patients showed blunted pupillary responses to reward, their subsequent saccade to the rewarding target reached the same peak velocity as non-apathetic patients and controls. Apathy thus attenuated reward sensitivity in both choices (**Chapter 2**) and pupil dilatation, without altering actual motor performance in either task.

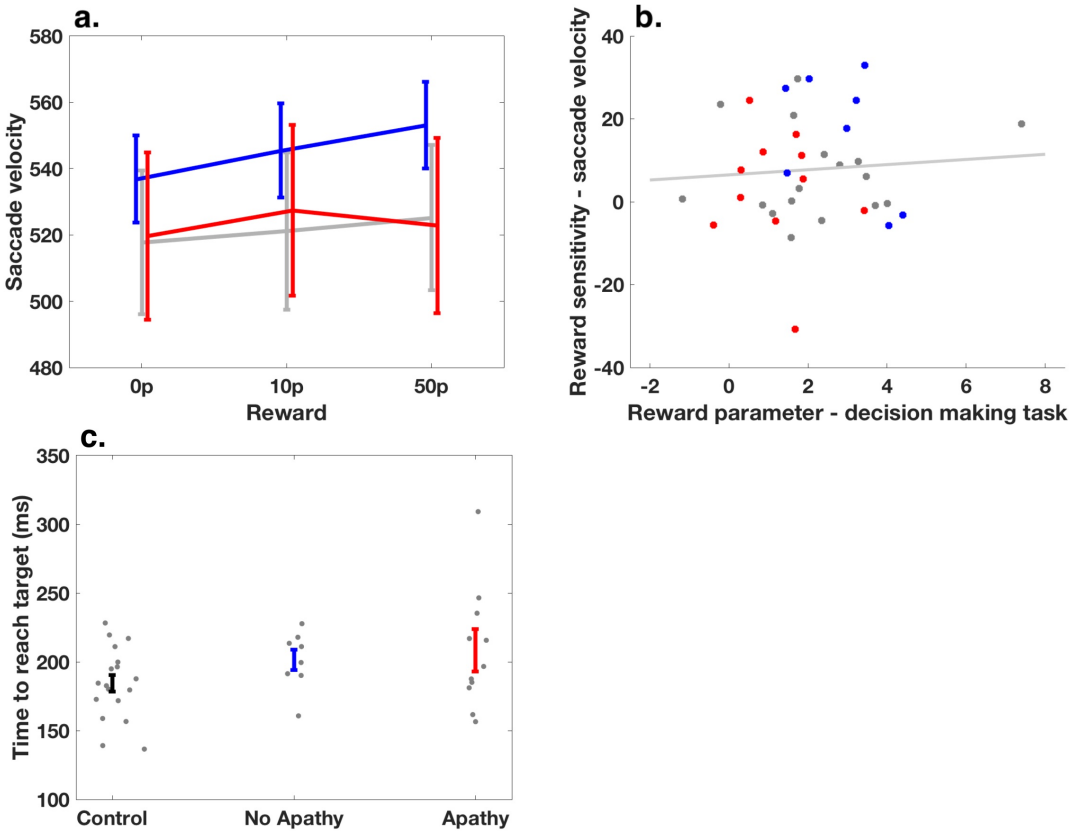


Figure 3-3. Apathy not associated with changes in saccade velocity or reaction time

There were no significant differences in peak saccade velocity between controls (grey), CADASIL no apathy (blue) or CADASIL apathy (red). There was a main effect of reward on velocity, with speed increasing with greater incentives (a). Reward sensitivity, indexed by change in saccade velocity with increasing incentives, was not correlated with the parameter estimate for reward from the behavioural decision making task (b). Reaction time (time to saccade to target following cue to move) did not differ as a function of apathy (c).

3.4 Experiment TWO: Reduced white matter tract integrity associated with apathy in CADASIL

3.4.1 Methods

Participants

Of the 19 CADASIL patients who underwent the behavioural study (**Chapter 2**), 18 also underwent an MRI scan, either on the same day as behavioural testing, or within a one month period. One patient declined due to claustrophobia. Additionally, two

further patients were excluded – one because of significant movement artefact during image acquisition, and the other due to an acute clinical event occurring between the behavioural testing and the time of imaging (which had been delayed by 1 month). This left 16 patients – 8 apathetic and 8 non-apathetic – for further analysis. Additionally, the 19 age and gender matched healthy controls described in the previous chapter also underwent the same imaging protocol, and 16 (those matched to the remaining patients) were used as the control group for the imaging analysis.

Imaging protocol

Participants were scanned in a 3T Siemens Verio scanner with a 12-channel head coil. The neuroimaging protocol included diffusion-weighted, T1-weighted and T2-weighted sequences. Whole-brain diffusion weighted imaging was performed using an echo-planar sequence (repetition time (TR) = 8900ms, echo time (TE) = 91.2ms, voxel size = 2mm isotropic, b-value = 1500s/mm^2). Images were obtained using diffusion-sensitising gradients in 60 isotropically distributed orientations optimised to evenly sample the whole diffusion sphere, acquired in opposite phase encoding directions (AP and PA) to allow for more robust distortion correction. 4 b=0 images were obtained in each phase encoding direction. High resolution whole brain T1-weighted images were acquired using a 3D MP-RAGE sequence (TR & TE=2000ms &1.94ms, flip angle 8^o, FOV = 256mm, voxel size 1mm isotropic). T2-weighted images were obtained using a clinical fluid-attenuated inversion recovery (FLAIR) sequence (TR & TE = 9000 & 88.0 ms, flip angle 150^o, FOV 192 mm, matrix size 174 x 192 x 50, voxel size 1 x 1 x 3 mm).

3.4.1.1 Image pre-processing and analysis

Pre-processing and analysis of Diffusion-weighted sequences

Correction for susceptibility induced distortions, eddy currents and subject movement: This was performed using the FSL tools *topup* and *eddy*. Diffusion data was collected with reversed phase-encode blips, resulting in pairs of images with distortions going in opposite directions. From these pairs the susceptibility-induced off-resonance field was estimated using a method similar to that described in (Andersson et al., 2003) as

implemented in FSL (Smith et al., 2004) and the two images were combined into a single corrected one. The output from *topup* was then passed to *eddy* (Andersson and Sotiropoulos, 2016) to correct for distortions associated with eddy currents and for subject movement.

Tract-based spatial statistics (TBSS):
Voxelwise statistical analysis of the FA data was carried out using TBSS (Smith et al., 2006). First, FA images were created by fitting a tensor model to the raw diffusion data using *DTIFIT* within FMRIB's diffusion toolbox (FDT). FA data from all subjects was then aligned into a common space (FMRIB58_FA) using the nonlinear registration *FNIRT* (Andersson et al., 2007). The mean (across all participants) FA image was then created and thinned to create a mean FA skeleton, representing the centre of all tracts common to the group. Each subject's aligned FA data was then projected onto this skeleton, and thresholded using a standard value of 0.2. Non-parametric voxelwise cross-subject statistics were then performed with *randomise* (Winkler et al., 2014) using threshold free cluster enhancement (TFCE) and 5000 permutations. TFCE p-value images (fully corrected for multiple comparisons across space) for CADASIL Apathy vs CADASIL No Apathy are reported in the results section.

Extraction of FA values from significant tracts:
To visualise the FA values of CADASIL subjects and healthy controls within the tracts which differed by apathy status, I used these white matter regions to define masks at each location and extracted mean FA values for each participant using *fslmeants*. I also extracted FA values from a control location – right inferior longitudinal fasciculus within the temporal pole (MNI coordinates: 48, 128, 47), a pathognomonic site for CADASIL lesions. Finally, as a global metric of white matter integrity the mean FA for each participant was extracted from their skeletonised image. Group differences in these variables were tested for using one-way ANOVAs.

Quantification and segmentation of white matter lesions

To quantify the total volume of while matter lesions, I used the automated *brain intensity abnormality classification algorithm* (BIANCA – Griffanti et al., 2016). The results for each participant were visually inspected to ensure appropriate segmentation.

BIANCA was run on brain-extracted FLAIR images using additional information from the T1 and diffusion-weighted sequence (FA and mean diffusivity (MD)). A training dataset previously obtained from a sporadic SVD cohort was used for this analysis (Griffanti et al., 2016). Because of differences in the location of white matter lesions between CADASIL and sporadic SVD (e.g. temporal poles), spatial co-ordinates (from the training dataset) were not inputted into the algorithm.

The steps for each participant involved:

- Eroding the cortical grey matter from the FLAIR image using the FSL script *make_bianca_mask,* which utilised the cortical cerebrospinal fluid (CSF) map extracted from the CSF-partial volume estimate obtained using FMRIB's automated segmentation tool (FAST - Zhang et al., 2001).
- Registering FA, MD and T1 images to FLAIR space
- Running BIANCA to obtain a white matter lesion map
- Binarising and inverting this map, using a threshold value of 0.1 (determined by visual inspection of matching between masks and lesions). Note that this is quite a lenient threshold, likely resulting in overestimation of WHM in the control group.
- Registering the binarised mask to T1 space, and re-binarising (because interpolation left some voxels with intermediate values) using a threshold of 0.8.

The total volume of white matter lesions for each participant was extracted from the mask using the script *bianca_cluster_stats,* and a one-way ANOVA was performed to test for differences between the controls and apathetic and non-apathetic CADASIL patients.

3.4.2 Results

White matter integrity – tract-based spatial statistics

Apathy was associated with significantly reduced FA in five major white matter tracts – left anterior cingulum, bilateral orbitofrontal-anterior cingulate white matter, right

anterior internal capsule, body of the corpus callosum and the left superior cerebellar peduncle (Figure **3-4**). There was also a significant reduction within a region of the right corona radiata. There were no regions where FA was significantly higher in apathetic compared to non-apathetic CADASIL patients.

Mean FA values extracted from these significant regions for the healthy controls and both patient groups suggested that disruptions in these white matter tracts were specific to the apathetic status of the CADASIL patients (**Figure 3-5**). Furthermore, apathetic and non-apathetic CADASIL patients did not differ in mean FA extracted across the entire TBSS skeleton (Mean Difference (FA) = 0.036, p=0.15). Rather, there was a general effect of disease with FA in both groups significantly lower than the controls: Mean Difference (No Apathy vs Controls) = 0.071, $p<0.001$; Mean Difference (Apathy vs Controls) = 0.11, $p<0.001$, **Figure 3-6**). Similarly, at the temporal pole control location (inferior longitudinal fasciculus) FA was also significantly lower in both apathetic and non-apathetic CADASIL patients compared to controls, but did not differ by apathy status (**Figure 3-6**).

Association between FA values and reward parameter estimate

Within the CADASIL patients there was a significant positive correlation between FA values extracted from each region and the behavioural reward sensitivity measure, within orbitofrontal-cingulate white matter and the anterior limb of the internal capsule (R=0.54, p=0.03; R=0.57, p=0.02, respectively). There was a trend towards a significant association with the anterior cingulum (R=0.41, p=0.1; **Figure 3-7**). There was also a significant association between these measures within the superior cerebellar peduncle (R=0.54, p=0.03). There was no significant association within the control region of inferior longitudinal fasciculus (R=-0.24, p=0.37). The above results remained if LARS score was included (in a linear regression), to orthogonalise the behavioural parameter with respect to apathy. None of the above correlations were significant if healthy control data was also included.

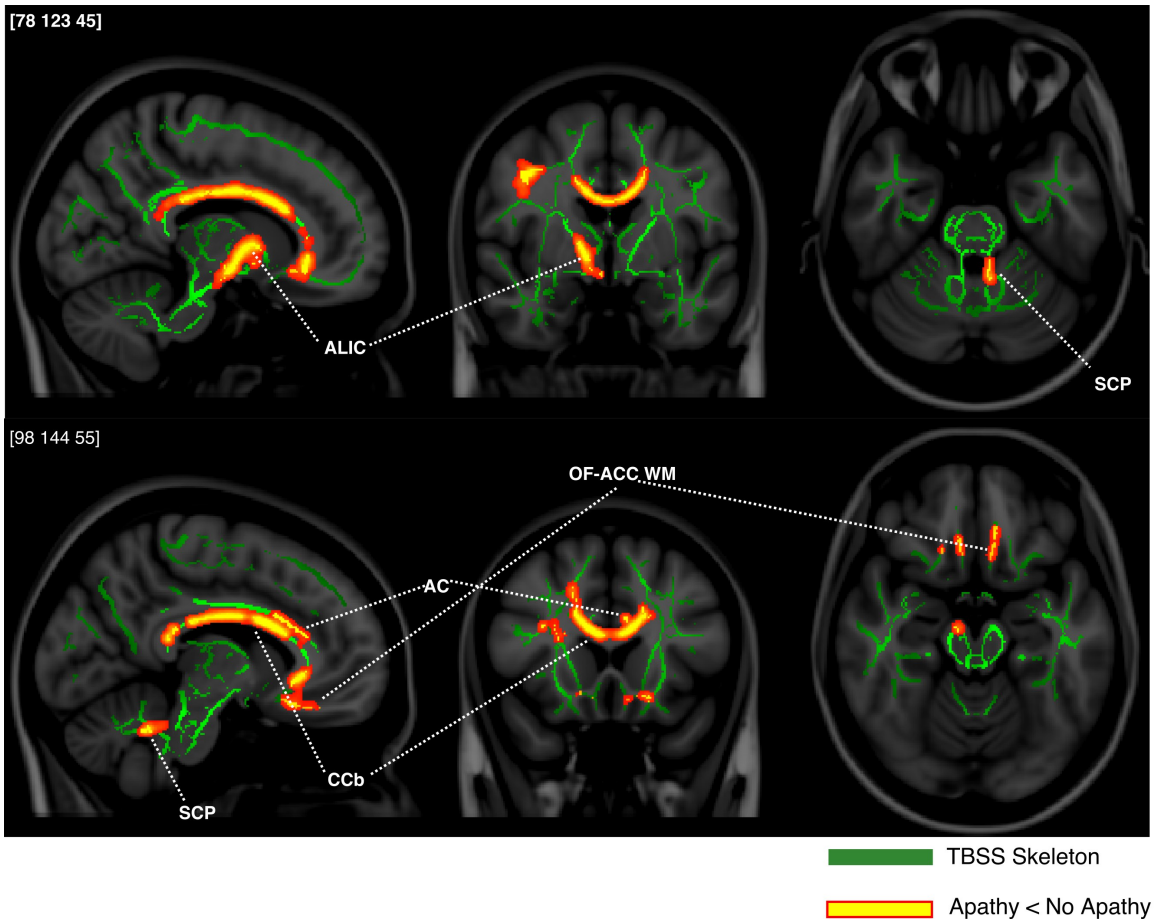


Figure 3-4. Regions where FA was reduced in CADASIL apathy

Apathetic CADASIL patients had significantly reduced white matter fractional anisotropy compared to non-apathetic CADASIL patients within the right anterior cingulum (AC), bilateral orbitofrontal-anterior cingulate white matter (OF-ACC WM), right anterior limb of the internal capsule (ALIC), body of the corpus callosum (CCb) and left superior cerebellar peduncle (SCP) – $p<0.05$, TFCE-corrected in red-yellow, against the study-specific white matter tract skeleton in green.

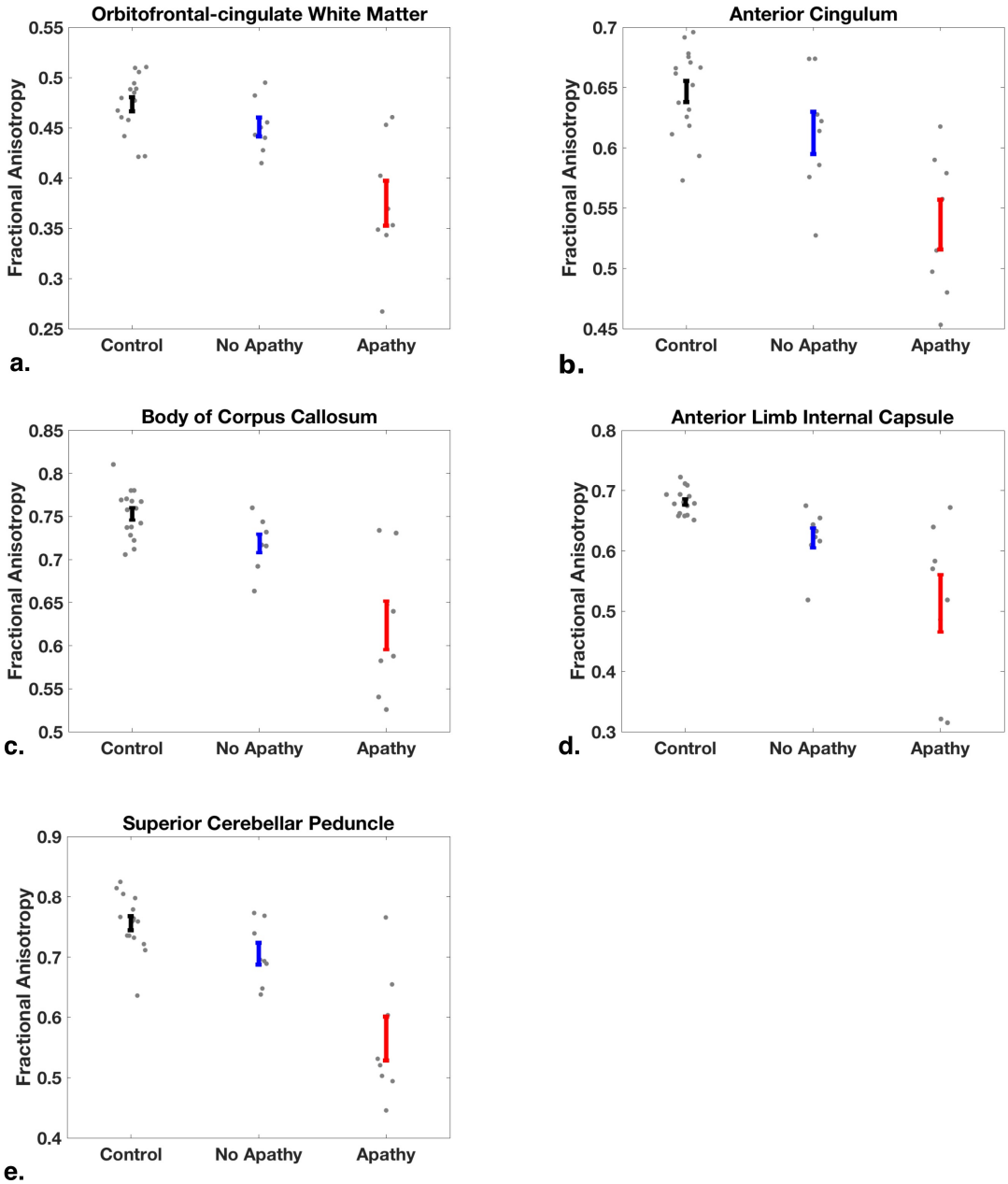


Figure 3-5. FA values in apathy-associated regions

(**a-e**) The errorbar plots ($Mean \pm SE$) show the average FA values from significant regions (from the apathy vs no apathy contrast) for control and CADASIL patients. FA in the apathy group appears to be reduced compared with both non-apathetic patients and controls at each location, whereas control and non-apathetic patient values overlapped considerably.

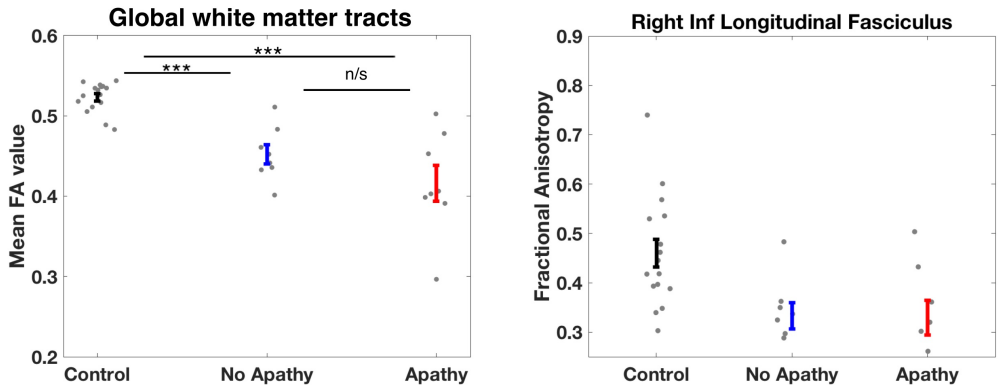


Figure 3-6. Global and control-region FA values

Global mean FA values were reduced in both apathetic and non-apathetic CADASIL patients compared to controls, but did not significantly differ from each other (**left panel**). A similar pattern was seen in the control location (temporal pole), with both CADASIL groups significantly reduced compared to controls, but no different from each other (**right panel**).

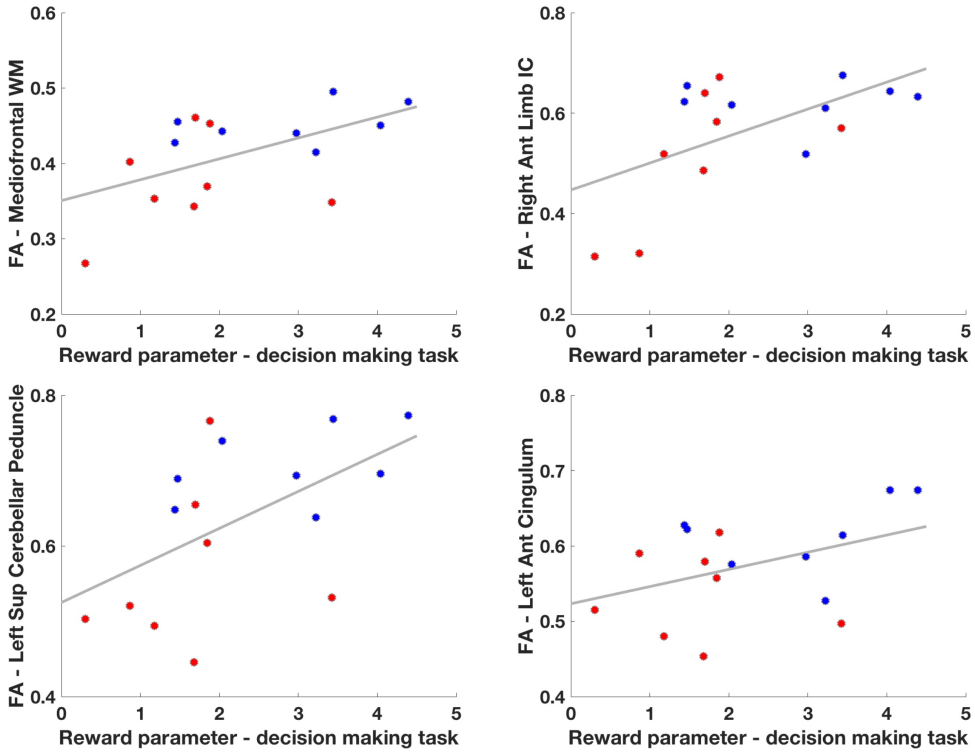


Figure 3-7. Significant association between FA and behavioural reward sensitivity

For the CADASIL patients, the metric of reward incentivisation from the decision making task was significantly associated with FA within orbitofrontal-cingulate white matter, anterior limb of the internal capsule and superior cerebellar peduncle, and trended towards significance within the anterior cingulum. Red dots: apathetic patients; blue dots: non-apathetic patients.

White matter hyperintensity volume

There was a significant effect of group on total WMH volume ($F(2,29)=12.6$, $p<0.001$). Both non-apathetic and apathetic CADASIL patients had significantly greater total WMH volume than controls (MD=67.1x10^3, p=0.001 & MD=71.7 x10^3, p=0.001 respectively) but importantly did not differ from each other (MD=4.5x10^3, p=0.97 (**Figure** 3-8). Therefore, the changes in white matter tract integrity associated with apathy seemed specific to the identified regions rather than being part of a more widespread process in the apathy group.

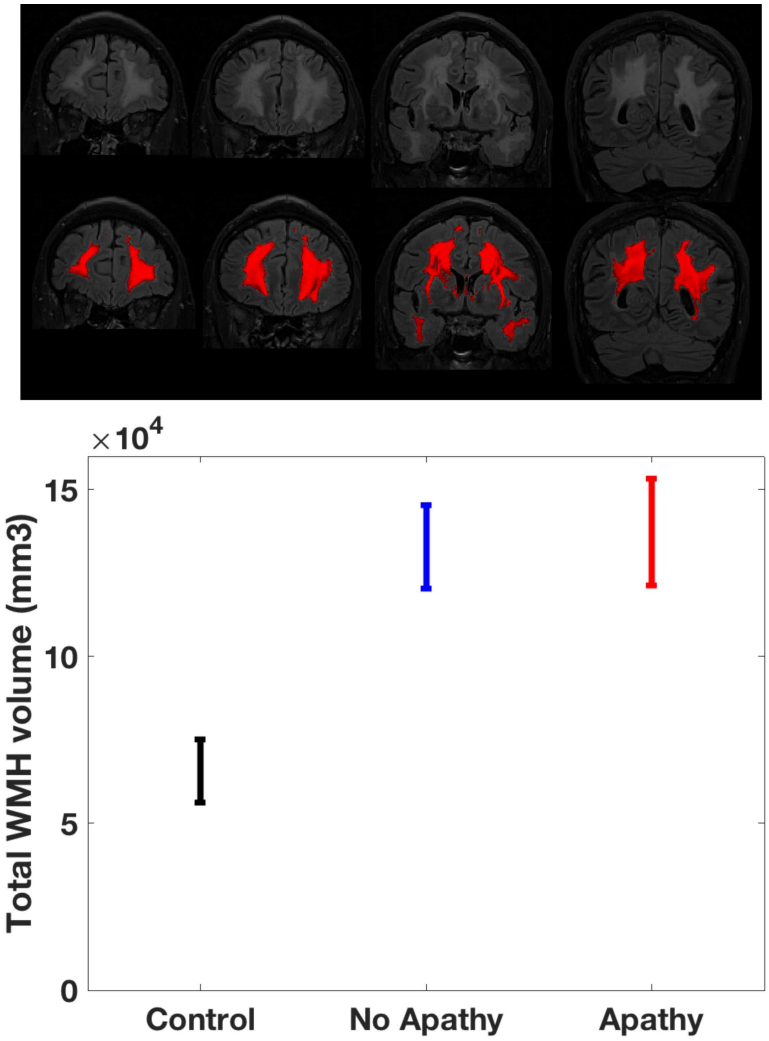


Figure 3-8. Total white matter hyperintensity volume in CADASIL and controls

A CADASIL patient's white matter lesion mask generated by BIANCA (red) is superimposed on their FLAIR (**top panel**). Both apathetic and non-apathetic CADASIL patients had a significantly higher volume of white matter hyperintensities than matched controls, but did not differ from each other (**bottom panel**).

3.5 Discussion

In these two investigations apathy in CADASIL was associated with blunted autonomic responses to reward and disruption of white matter tracts connecting neural regions crucial for reward processing and effort-based decision making. Furthermore, these changes related directly to the behavioural metric that defined disrupted effort-based decision making in apathetic CADASIL patients: reduced reward incentivisation. Therefore, this study provides the first evidence of both altered physiological responses and reduced white matter tract integrity in CADASIL apathy, and links these changes to disruption of a specific mechanism underlying normal goal directed behaviour.

The blunting of the normal pupillary response to reward in the apathetic group is particularly compelling given the behavioural result, in which patients showed changes along the same axis of effort-based decision making – incentivisation by reward. Furthermore, the significant correlation between the two markers of reward sensitivity (behavioural and autonomic) strengthens the claim that they are indeed measuring this reward metric. Importantly, the normal responses in the non-apathetic group demonstrate the pupil result is not simply a general feature of having CADASIL, nor could it be explained by other confounders such as age or gender, which were matched between groups. Rather, blunted pupillary responses to reward were a specific feature of the apathetic state. This suggests that other findings of reward insensitivity associated with PD apathy may also be relevant to CADASIL (Lawrence et al., 2011; Martinez-Horta et al., 2014b; Muhammed et al., 2016), and more broadly fits with a transdiagnostic model of apathy, in which it occurs secondary to disruption of specific underlying cognitive mechanisms (here reward processing within effort-based decision making), regardless of the underlying disease (Le Heron et al., 2017).

It is also notable that not all aspects of the reward related response were significantly altered in patients with apathy. Specifically, peak saccadic velocities to the rewarding target were no different compared to either non-apathetic patients or healthy controls. This mirrors the findings associated with apathy in PD, where the apathetic patients also showed blunted pupillary responses but preserved saccadic velocities (Muhammed

et al., 2016). Apathy thus attenuated reward sensitivity in both choices (**Chapter 2**) and pupil dilatation, without altering actual motor performance in either task. One frequently emphasised feature of apathy is that it is a failure of *self-generated* goal directed behaviour (Levy and Dubois, 2006; Robert et al., 2009; Sockeel et al., 2006). In the paradigm used here, saccadic eye movements were *externally cued* (by the target appearing and fixation point disappearing), which may have effectively bypassed the disrupted mechanisms underlying apathy. This demonstrates that not all components of effortful behaviour for reward are disrupted in apathy and points to a potentially important, simple therapeutic strategy – providing external cues or prompts for action within an apathetic patient's environment.

Anatomically, apathy was associated with reduced white matter integrity within specific white matter tracts – anterior cingulum, orbitofrontal-cingulate white matter, anterior limb of the internal capsule and the body of the corpus callosum – tracts that connect brain regions strongly implicated in effort-based decision making (Hauser et al., 2017; Klein-Flugge et al., 2016; Neubert et al., 2015; Prevost et al., 2010). Furthermore, non-apathetic patients did not appear to differ from healthy controls in these regions. That is, damage to these tracts was specifically associated with apathy rather than CADASIL more generally, mirroring the behavioural and physiological findings. Furthermore, FA values in OFC-ACC white matter and the ALIC (as well as the superior cerebellar peduncle) also correlated with the behavioural reward sensitivity parameter. In contrast, apathy was not associated with overall burden of white matter disease (assessed by either each participant's mean global FA value or WMH burden), nor with significant changes in FA (compared to non-apathetic CADASIL patients) in a control region not associated with effort-based decision making. Instead these metrics were altered as a function of disease itself.

These anatomical findings are consistent with studies of apathy in different conditions. The *anterior cingulum* is closely associated with the overlying anterior cingulate cortex, and reduced FA within this tract has been linked to apathy in sporadic SVD (Hollocks et al., 2015) and Alzheimer's disease (Kim et al., 2011), as well as reduced motivation in healthy people (Bonnelle et al., 2016). The identified ventral white matter region associated with orbitofrontal and anterior cingulate cortex (*OFC-ACC*) lies medial to the uncinate fasciculus and may represent the amygdalofugal pathway, a

tract that links amygdala and regions including ventral striatum and medial frontal cortex (Kamali et al., 2016; Miller et al., 2010; Mori et al., 2017). The *anterior limb of the internal capsule* contains fibres projecting between anterior and mediodorsal thalamus and prefrontal and anterior cingulate cortex. Thalamic strokes within these regions are an important subcortical cause of apathy (Carrera and Bogousslavsky, 2006). Reduced FA in the *body of the corpus callosum* has been associated with apathy in progressive supranuclear palsy (Agosta et al., 2014). Furthermore, the medial cortical and subcortical regions connected by these tracts have been consistently associated with apathy across multiple disorders and imaging modalities (Huang et al., 2013; Lanctôt et al., 2007; Le Heron et al., 2017; Schroeter et al., 2011). It is within these regions that the core processes of effort-based decision making to drive motivated behaviour are thought to be instantiated (Croxson et al., 2009; Kennerley et al., 2009; Le Heron et al., 2017; Levy and Glimcher, 2012; Migneco et al., 2001; Rushworth et al., 2012; Schroeter et al., 2011). It remains unclear the significance of the association in the *superior cerebellar peduncle*. The *superior cerebellar peduncle* contains both efferent and afferent fibre tracts, connecting to spinal cord, regions of the brain stem and thalamus. Although degeneration of this region has been associated with some neurological conditions (e.g., progressive supranuclear palsy, Sako et al., 2017), its significance for apathy remains unclear. The impact of cerebellar damage on cognition and behaviour has received growing attention over recent decades (Schmahmann and Sherman, 1998) but a precise understanding of its role in cognition and particularly in motivated behaviour is currently lacking.

One potential caveat to these interpretations is the small number of patients involved in the study. Reported correlations in particular should therefore be interpreted with some caution. However, CADASIL is a relatively rare disorder (Chabriat et al., 2009) and there is no reason to consider the sampled population was unrepresentative. Furthermore, studying a smaller group enabled an in-depth strategy to investigate mechanisms underlying apathy from behavioural, physiological and anatomical perspectives in the same cohort. Additionally, CADASIL provides a unique model to investigate the effects of pure vascular cognitive impairment, free from potential confounders such as co-existent neurodegenerative pathology (Attems and Jellinger, 2014; Charlton et al., 2006). The consistency of the imaging results with previous work supports the general coherence of these findings, as does the strong parallels between

the behavioural and physiological responses of apathetic CADASIL patients and apathetic Parkinson's disease patients performing the same tasks (Muhammed et al., 2016 & **Chapter 4**). While I have focussed on white matter integrity in this study because it is the primary site of pathology in CADASIL, future work could profitably investigate the consequences of these disruptions, for example examining whether reduced functional connectivity between implicated regions is associated with apathy.

Apathy in CADASIL is characterised by reduced incentivisation by rewards, whether measured behaviourally or physiologically, and disruption of connections between neural regions that process and integrate reward and cost information to motivate actions. These disruptions of normal effort-based decision making manifest as a reduction in goal directed behaviour, the defining clinical feature of the apathetic syndrome. Relating apathy to dysfunction of underlying cognitive mechanisms advances our understanding of this debilitating syndrome, and, as discussed in **Chapter 7**, points to potential therapeutic strategies to explore in the future.

4 Distinct effects of apathy and dopamine on effort-based decision making in Parkinson's disease

4.1 Chapter Summary

Effort-based decision making is a cognitive process crucial to normal motivated behaviour. Apathy is a common and disabling complication of Parkinson's disease, but its aetiology remains unclear. Intriguingly, the neural substrates associated with apathy also sub-serve effort-based decision making in animal models and humans. Furthermore, the dopaminergic system plays a core role in motivating effortful behaviour for reward, and its dysfunction has been proposed to play a crucial role in the aetiology of apathy in Parkinson's disease. In this chapter I investigate whether disrupted effort-based decision making underlies the syndrome of apathy in Parkinson's disease, and if this disruption is modulated by the dopaminergic system. Using the same behavioural task as in the CADASIL study, I tested 39 patients with Parkinson's disease, with and without clinical apathy, ON and OFF their normal dopaminergic medications across two separate sessions, as well as 32 healthy age- and gender-matched controls. The primary outcome variable was choice (accept/decline offer) analysed using a hierarchical generalised linear mixed effects model, and the vigour of squeeze (Newtons exerted *above* required force). The results demonstrate that while both apathy and dopamine depletion are associated with reduced acceptance of offers, these effects are driven by dissociable patterns of responding. While apathy was characterised by increased rejection of predominantly low reward offers, dopamine increased responding to high effort, high reward offers, irrespective of underlying motivational state. Dopamine also exerted a main effect on motor vigour, increasing force production independently of reward offered, while apathy did not affect this measure. The findings demonstrate that disrupted effort based decision making underlies Parkinson's disease apathy, but in a manner distinct to that caused by dopamine depletion. Thus the motivational deficit observed in Parkinson's disease appears not to be simply secondary to dopaminergic depletion of mesocorticolimbic pathways, suggesting *non-dopaminergic* therapeutic strategies for apathy may be important future targets.

4.2 Introduction

Deciding if an action – or sequence of actions – is *"worth it"* is a cognitive process lying at the core of motivated goal directed behaviour (Balleine and O'Doherty, 2010; Mogenson et al., 1980; Salamone et al., 2016). Often termed effort-based decision making, the crucial evaluation is whether the rewarding outcomes of a potential behaviour outweigh its associated action costs (Kurniawan et al., 2011). Although time delays and reward probability also determine the overall cost, there is good evidence that effort-related costs (whether physical or cognitive) are processed and integrated with reward information in distinct brain areas to drive choice (Trevor Chong et al., 2017a; Hauser et al., 2017; Klein-Flugge et al., 2016; Prevost et al., 2010; Rudebeck et al., 2006; Rushworth et al., 2012).

In Parkinson's disease (PD), apathy is a frequent and disabling complication (Aarsland et al., 2009; Martinez-Fernandez et al., 2016). Apathetic patients often report *"I just can't be bothered"* but a mechanistic understanding of this syndrome remains elusive. Although apathy has been conceptualised as a disorder of goal directed behaviour for many years, a more robust understanding of its underlying neurocognitive mechanisms is lacking (Levy and Dubois, 2006; Marin, 1991; Starkstein and Leentjens, 2008). In PD, apathy is associated in particular with reduced metabolism within ventral striatum (VS), medial frontal cortex including dorsal anterior cingulate cortex (dACC) and ventral midbrain (Huang et al., 2013; Lawrence et al., 2011; Robert et al., 2014), reduced grey matter volume of ventral striatum (Carriere et al., 2014), and reduced functional connectivity between these brain regions (Baggio et al., 2015). Strikingly, these are the same brain areas demonstrated to underlie effort-based decision making in healthy humans (Croxson et al., 2009; Hauser et al., 2017; Klein-Flugge et al., 2016; Le Heron et al., 2017; Prevost et al., 2010). Furthermore, in experimental animal models disruption of homologues of these regions induces a seemingly apathetic state, in which animals are *no longer as willing to invest effort for reward* (Hauber and Sommer, 2009; Walton et al., 2002).

Aside from these anatomical considerations, there is some evidence that effort-based decision making and PD apathy might also share a common association with the neuromodulatory dopaminergic system. Dopamine projections from the ventral

tegmental area (VTA) particularly to VS and medial frontal cortex play a crucial role in effort based decision making, signalling the value of potential actions to drive appetitive/approach behaviours for reward (Hamid et al., 2016; Kurniawan et al., 2011; Salamone et al., 2016; Salamone and Correa, 2012; Syed et al., 2016). Disruption of this system with dopamine antagonists produces similar effects on effort based decision making as lesions to these regions, biasing animals away from high effort for high reward options (Salamone et al., 2007). Reduced mesolimbic dopamine has also been hypothesized to contribute to apathy in PD. These patients show reduced VS dopamine binding capacity, as well as blunted dopamine release following administration of methylphenidate, compared to PD patients without apathy (Remy et al., 2005; Santangelo et al., 2015; Thobois et al., 2010).

Such findings have motivated therapeutic trials of dopamine replacement for PD apathy. However, results to date have been mixed and interpretation confounded by factors such as dopamine withdrawal following deep brain stimulation (Chung et al., 2016; Thobois et al., 2013). Thus it remains unclear whether alterations in the dopaminergic system alone are responsible for the loss of motivation observed in PD apathy. Indeed, recent findings point to a potential role for *non-dopaminergic* modulation of apathy in PD, involving the serotonergic and cholinergic systems (Devos et al., 2014; Maillet et al., 2016). Effort-based decision making in healthy people has also been shown to be affected by a serotonin reuptake inhibitor (Meyniel et al., 2016), whilst an important role for adenosine A_{2A} receptors in this process has been demonstrated in rodents (Nunes et al., 2013). These findings raise the possibility that non-dopaminergic neurotransmitter systems normally play an important role in guiding such behavior (Salamone et al., 2016).

Here, I investigate the relationship between effort-based decision making and PD apathy, as well as the impact of dopamine therapy, within the same experimental framework. I hypothesize that disruption of effort based decision making – specifically the mechanism by which individuals weigh up rewards and costs associated with a potential action or sequence of actions – provides a plausible explanation for the reduced goal directed behaviour that defines apathy in PD. Furthermore, by examining patients ON and OFF their dopaminergic medication, I investigate whether this

disruption in effort-based decision making might indeed be mediated by alterations in dopaminergic tone.

The findings of some recent studies provide further motivation for this approach. It has been shown that apathy in PD is associated with reduced autonomic (Muhammed et al., 2016) and electrophysiological (Martinez-Horta et al., 2014a) responses to reward, consistent with a failure of incentivisation by reward. However, those studies did not examine decision making based on weighing up the effort required to obtain a particular reward. In Chapter two I demonstrated that altered effort-based decision making is associated with apathy in CADASIL. Although the underlying pathology in PD and CADASIL is quite distinct, the clinical phenotype of apathy is broadly very similar, suggesting a common mechanism (such as disrupted decision making) could underlie it (Le Heron et al., 2017). It has also been reported that PD patients when tested ON dopaminergic medication are prepared to exert *more effort for a given reward* than when OFF medication (after an overnight withdrawal of these drugs) (Chong et al., 2015; Le Bouc et al., 2016). However, patients in those studies had normal levels of motivation and it is unclear whether these findings would translate into a group who are clinically apathetic, or whether in fact the motivational effects of dopamine occur on a separate axis to the deficits that underlie apathy. This is important because apathetic behaviour might result either from *hypersensitivity to the effort costs of actions*, *insensitivity to the rewarding outcomes of actions* (as was demonstrated in CADASIL) or a combination of both. Moreover, the effects of dopamine might be different to the effects of apathy.

In this study I administered an effort-based decision making task to PD patients with and without clinical apathy, ON and OFF their normal dopaminergic medications, to assess the independent effects of these factors on effort-based decision making, as well as the interaction between the two. Furthermore, the experimental design (as with the CADASIL study) allowed me to dissociate the distinct effects of effort and reward on choice behaviour within a biologically relevant decision space. This potentially provides a deeper mechanistic understanding of any differences identified, and also enables translation of findings back to everyday behaviour. Specifically, I investigated whether changes in effort-based decision making associated with apathy, and being OFF dopamine, manifest globally across decision space (e.g., as a generalised

reduction in engagement with the task) or whether these factors have more specific, dissociable effects. Using this approach I examined whether dopamine and apathy have the same or distinctly different effects on effort-based decision making.

4.3 Methods

4.3.1 Ethics

The study was approved by the local ethics committee and written consent was obtained from all subjects in accordance with the Declaration of Helsinki.

4.3.2 Participants

Forty one patients with a clinical diagnosis of idiopathic PD (confirmed by two neurologists including myself) were recruited from local movement disorders clinics in the Oxfordshire area. Inclusion criteria included an absence of PD dementia or other major neurological or psychiatric conditions, although the presence of depression was not a specific exclusion factor. I specifically aimed to recruit an even sample of apathetic and non-apathetic patients. Two patients were subsequently excluded – one due to a failure to understand the task, and one who did not attend the second session, leaving 39 patients. 32 healthy age and gender-matched controls were recruited via a local database. All patients were tested in two morning sessions, one ON their normal dopaminergic medications and the other having withheld these since the night before (OFF), counter-balanced across apathy status.

Disease, cognitive and questionnaire measures

Apathy was assessed by standardised clinical interview with the patient, using the Lille apathy rating scale which has previously been validated in PD (Sockeel et al., 2006). Patients were classified as apathetic if their LARS score was > -22 (a cut-off corresponding to at least mild-moderate apathy levels). Severity of PD was assessed using the Unified PD rating scale (UPDRS) total score (Goetz et al., 2008) and Hoehn and Yahr stage. The UPDRS-III (motor score) was repeated in the ON and OFF states. As a baseline cognitive screen, all subjects were administered the Addenbrooke's cognitive examination version III (ACE-III) (Hsieh et al., 2013), and a digit span task

to assess working memory (Groth-Marnat, 2000), in the ON state. Depressive symptoms were assessed using the Beck Depression Inventory-II (BDI-II) (Beck et al., 1996). A separate dysphoria-only subscale of the BDI-II was also calculated, given the potential for overlap between apathy and anhedonia components of depression (Kirsch-Darrow et al., 2011; Treadway and Zald, 2011). Quality of life (QOL) was assessed using a Cantril ladder (Cantril, 1965). Demographics are displayed in **Table 4-1**.

4.3.3 Experimental design

The behavioural paradigm has already been described (**Chapter Two**), although for clarity is reproduced (**Figure 4-1)**. Of note, each participant's maximal voluntary contraction (MVC) was calculated separately for each hand and session, so all responses were normalised to each individual for each session of testing.

In addition to choice (accept/reject), decision latency and force metrics (sampled at 500Hz) were recorded for each trial. I used the peak force exerted on each trial (in Newtons) as a measure of motor vigour (Le Bouc et al., 2016), normalising this value across effort levels by subtracting the minimum required force level for that particular trial (**Figure 4-1d**). Following the experiment participants rated how physically challenging they found each of the effort levels on a 21-point visual rating scale.

Measure	Healthy elderly controls	Parkinson's disease	Control vs Parkinson's disease (p value)	Parkinson's disease – no apathy (LARS < -22)	Parkinson's disease – apathy (LARS ≥-22)	No apathy vs apathy (p value)
Number	32	39	n/a	18	21	n/a
Age	68.9 (±6.9)	67.8 (±7.6)	p=0.55	68.2 (±6.5)	67.5 (±8.5)	p=0.78
Gender (F/M)	13/19	12/27	p=0.39^	8/10	4/17	p=0.16^
Apathy (LARS)	-28.3 (±3.1)	-20.9 (±6.8)	**p<0.0001**	-27 (± 3.8)	-15.7 (±3.8)	**p<0.0001**
Hoehn & Yahr stage	n/a	2.2 (±0.51)	n/a	2.1 (±0.6)	2.2 (±0.4)	p=0.44
UPDRS - total	n/a	82.3 (26.6)	n/a	73.8 (±25.7)	89.9 (±25.7)	p=0.08
UPDRS motor score ON	n/a	28.4 (±11.4)	n/a	27.1 (±13.2)	29.5 (±9.9)	p=0.5
UPDRS motor score OFF	n/a	35.9 (±10.8)	n/a	32.7 (±11.0)	38.7 (±10.2)	p=0.09
Change in motor score	n/a	7.5 (±8.3)	n/a	5.7 (±8.3)	9.1 (±8.1)	p=0.2
Levodopa equivalent dose (mg/24 hours)	n/a	633 (±356)	n/a	565 (±353)	691 (±357)	p=0.27
Hours since last dose – OFF	n/a	18 (±3)	n/a	19 (±3)	17 (±3)	**p=0.04**
Hours since last dose – ON	n/a	2.3 (±1.5)	n/a	2.7 (±1.6)	2 (±1.4)	p=0.19
Depression (BDI-II)	3.8 (±3.7)	14.3 (±7.7)	**p<0.0001**	11 (±7.0)	17.1 (±7.4)	**p=0.01**
Dysphoria sub-scale	1.1 (± 1.5)	4.9 (±4.0)	**p<0.0001**	4.4 (±4.2)	5.3 (±3.8)	p=0.53
Global Cognition (ACE)	95.6 (±3.8)	91.1 (±7.9)	**p=0.005**	93.5 (±5.0)	89.4 (±9.4)	p=0.08
Quality of life	8.0 (±1.2)	6.7 (±1.8)	**p=0.001**	7.6 (±1.5)	6.0 (±1.8)	**p=0.01**
Digit span	20.6 (±4.4)	17.4 (±3.6)	**p=0.002**	16.7 (±3.1)	17.9 (±3.9)	p=0.35

Table 4-1. Demographic, questionnaire and baseline cognitive measures LARS – Lille apathy rating scale; UPDRS – Unified Parkinson's disease rating scale; BDI-II – Beck's depression inventory II; ACE – Addenbrooke's cognitive examination III; Quality of life – Cantril ladder (range 0-10); ^chi-squared test; (all values are mean +/- standard deviation)

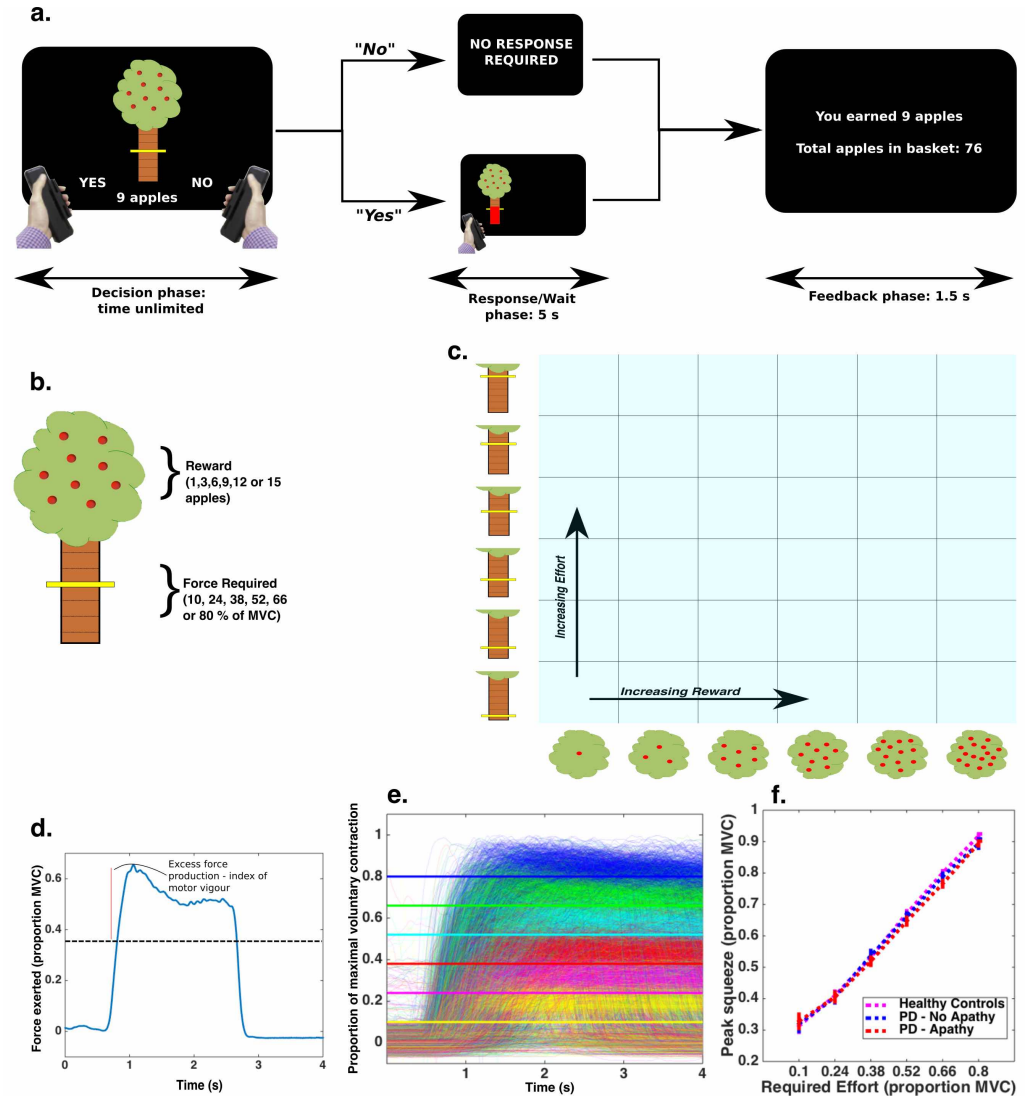


Figure 4-1. Effort-based decision making task

(**a**) On a trial-by-trial basis participants were presented with offers of a certain amount of reward (apples on an apple tree, with each apple worth 1p) in return for a level of physical effort (ranging between 10% and 80% of a subjects' previously-determined maximal voluntary contraction, held for 1 second (**b**). They were instructed to weigh up each offer, deciding *"whether it was worth it"*. If they accepted an offer (by squeezing the left-hand grip) the tree moved to the left or right of the screen, indicating which hand they had to perform the force squeeze with. They had a 5 second window within which to achieve the required force level. If they rejected the offer (by squeezing the right-hand grip) they waited the same 5 second period. After a feedback phase they then moved onto the next trial. (**c**) After a practice session, participants worked through 180 trials, which evenly sampled the 6 x 6 *'decision space'* over 5 blocks. (**d**) Example force trace from a single trial. Motor vigour was indexed by *excess* force generated above the required effort level, i.e. how much more than was required that a participant squeezed. (**e**) Participants parametrically modulated force output to task requirements. Superimposed force traces for all patients, ON and OFF their dopaminergic medications. Each required force level is a different colour, and the solid lines show the minimum required level. (**f**) Both patients and healthy controls modulated squeeze force appropriately.

4.3.4 Statistical analysis

The primary outcome of this study was choice (accept/reject), and how this varied across the reward/effort decision space between apathetic and non-apathetic patients, ON and OFF their normal dopaminergic medications. Data was analysed within Matlab (MathWorks, USA) using custom scripts. Trials where decision time was less than 0.4 seconds were discarded as accidental squeezes. As the primary analysis method I used a generalised linear mixed effects model (with a binomial link function and Laplace fit method) to model accept/reject responses (*fitglme* within Matlab). This meant every valid trial was included in the model. This allowed me to:

1) Apply a nonlinear (logistic) transform to the choice data, which was clearly not normally distributed
2) Assess all variables of interest (and their potential interactions) within a single model
3) Account for the effects of inter-subject variability (by modelling the random effect of subject)

The model included a random effect of subject and fixed effects of reward, effort, apathy status and dopamine state. It also included a main effect of session (1^{st} or 2^{nd}) as this parameter significantly improved model fit (change in AIC units = 14). Notably, a session*drug interaction term (ON-OFF vs OFF-ON order) was not significant and worsened model fit ($p= 0.48$, change in AIC units = 1.5) and was not included in the model. The inclusion or exclusion of the session and session*drug terms did not affect any other results.

My main approach was to first fit the full model (including all interactions between reward, effort, apathy and dopamine). I compared this model to all other possible combinations, using the Akaike Information Criterion (AIC). No model improved fit by more than 2 AIC units (a standard cut-off level, Burnham and Anderson, 2004), and therefore the full model results are reported (raw and modelled choice proportion estimates are shown in **Figure 4-2**). Here I report the t-statistic, F statistic and p value associated with each parameter estimate. All statistical tests were two-tailed, using an alpha-level of $p < 0.05$.

Additionally, to answer the initial question of whether there was an overall difference in offer acceptance associated with either apathy or dopamine depletion I used the proportion of offers accepted as a raw measure of task performance. The baseline effect of apathy on choice was examined with subjects in their normal ON state, using a one-way ANOVA for the 3 groups (healthy controls, **HC**; PD non-apathetic cases, **PD-NoA**; PD-apathetic cases, **PD-A**). The main effect of dopamine on this metric was calculated using a paired t-test of change in proportion acceptance ON versus OFF. Change in motor vigour was analysed using a repeated measures ANOVA with dopamine as a within subject variable, apathy between subject and force (Newtons) the dependent variable. Tests for differences in demographic factors between groups were performed using standard unpaired t-tests, or, when it was of interest to include HC, PD-NoA and PD-A together, a one-way ANOVA.

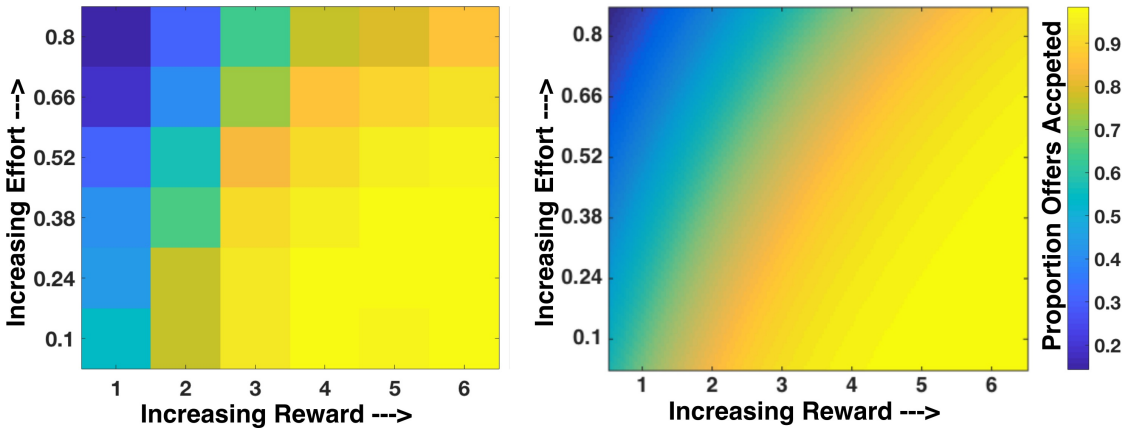


Figure 4-2. Modelled data closely approximated raw choices.

Proportion of accepted offers for raw (left) and modelled (right) data. Data is from all choices made by the 39 PD patients, across both ON and OFF sessions

4.4 Results

4.4.1 Clinical apathy and dopamine depletion reduce offer acceptance

I first assessed the raw effects of clinical apathy on choice by comparing group performance in the ON state. There was a significant main effect of group (HC, PD-NA and PD-A) on number of offers accepted ($F(2,68) = 8.12$, $p = 0.001$). Apathetic PD patients accepted significantly fewer offers than *both* healthy controls (mean difference in proportion of offers accepted 0.15, $t(51)=4.01$, $p<0.001$) and non-apathetic PD patients (mean difference 0.10, $t(37)=2.33$, $p=0.029$) across the experiment. There was no significant difference between non-apathetic PD patients and healthy controls (mean difference 0.049, $t(48)=1.3$, $p=0.20$, **Figure 4-3a**). Task performance correlated most closely with the action initiation (AI) subscale of the LARS ($r = 0.37$, $n=39$, $p = 0.019$**, Figure 4-3b**). Thus the more apathetic an individual was with respect to action initiation, the less likely they were to accept an offer on the task. This association could not be explained by motor deficit, with no significant relationship between acceptance rate and UPDRS-motor score ($R=0.14$, $N=39$, $p=0.38$).

Dopamine depletion in these PD patients, as indexed by performance when OFF dopaminergic drugs, also reduced offer acceptance. Patients accepted significantly more offers when ON compared to OFF their usual dopaminergic medications (mean increase ON dopamine 6% (SEM 2.4%), $t(38)=2.45$, $p=0.019$). Interestingly, although dopamine depletion reduced offers accepted overall, this effect was quite heterogeneous in the population, with some individuals (from both sides of the apathy spectrum) actually accepting more offers in the OFF state (**Figure 4-3c**). In contrast to the apathy effect, there was no correlation between the AI subscale of the LARS and effect of dopamine on acceptance rate ($R=0.06$, $n=39$, $p=0.71$). These findings therefore show that *both* apathy and being OFF dopaminergic medication reduce the willingness to invest effort for reward.

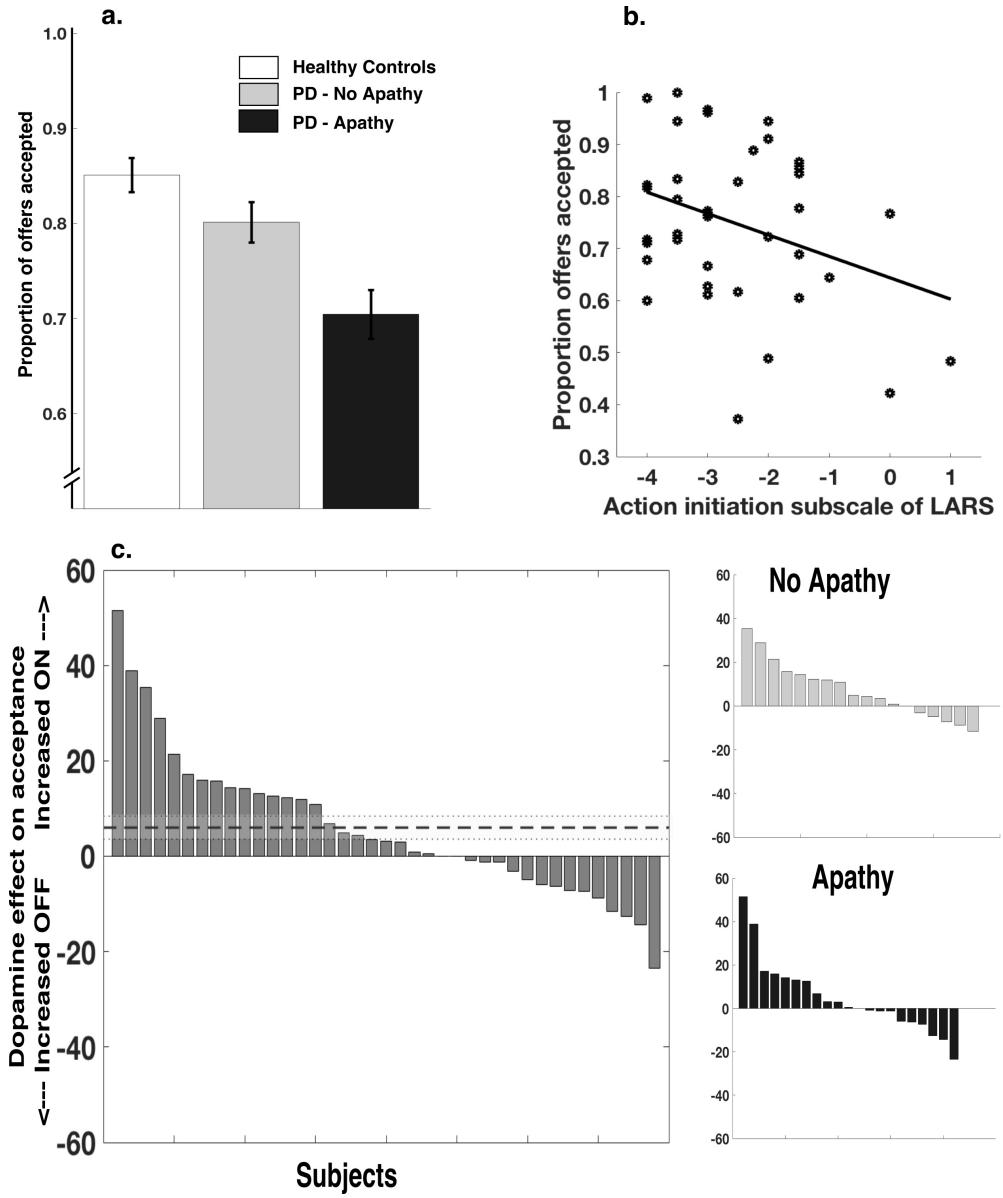


Figure 4-3. Raw acceptance rate as apathy and dopamine varied

(**a**) Apathetic PD patients accepted significantly fewer offers than healthy controls or non-apathetic PD patients (errorbars are +/- SEM). (**b**) Apathy level (Action Initiation subscale of LARS) strongly correlated with acceptance rate (r=0.37, p=0.019; ON state shown). (**c**) Dopamine depletion (OFF state) was associated with significantly reduced acceptance rates, *irrespective* of apathy status (dotted line is mean effect +/- SEM).

4.4.2 Distinct interactions drive reduced responding in apathy and dopamine depletion

I next aimed to determine the driving factors behind the reduced responding associated with both apathy and dopamine depletion using the generalised linear mixed effects model described in the Methods section. There were two significant, independent 3-way interactions:

Apathy * Reward * Effort ($t = 3.02$; $F(1,39) = 9.15$; $p = 0.004$)
Dopamine * Reward * Effort ($t = -3.14$; $F(1,39) = 9.84$; $p = 0.003$)

These indicate that the effects of apathy and dopamine on choice were *not* constant throughout decision space. Instead, *apathy reduced responses for low reward offers*, *particularly when effort costs were lower*, whilst dopamine depletion reduced responses for *high effort, high reward* offers (**Figure 4-4**). In addition to these effects, there were significant main effects of reward ($t = 43$; $F(1,39) = 1849$; $p < 0.0001$), effort ($t = -26.4$; $F(1,39) = 701$; $p < 0.0001$), dopamine ($t = -3.38$; $F(1,39) = 11.4$, $p < 0.0016$), and session ($t = 4.79$, $F(1,39) = 22.95$, $p < 0.0001$), although not apathy ($t = -1.49$; $F(1,39) = 2.23$, $p = 0.14$), as well as a significant Dopamine * Effort interaction ($t = -2.87$; $F(1,39) = 8.24$, $p = 0.0066$), Apathy * Effort interaction ($t = 2.57$; $F(1,39) = 6.58$, $p = 0.014$) and Reward * Effort interaction ($t = -7.89$; $F(1,39) = 62.3$, $p < 0.0001$). There were no significant 2-way interactions between reward and apathy ($p = 0.63$ – although this interaction was strongly significant if the apathy*reward*effort term was removed), reward and dopamine ($p = 0.12$), or apathy and dopamine ($p = 0.55$), nor were the apathy*dopamine*effort, apathy*dopamine*reward interactions, or the full 4-way interaction significant ($p = 0.09$, $p = 0.75$ and $p = 0.27$ respectively) – Table 4-2, plus see **Appendix 3** for graphical illustration of these factors and for the choice data split by reward and effort level.

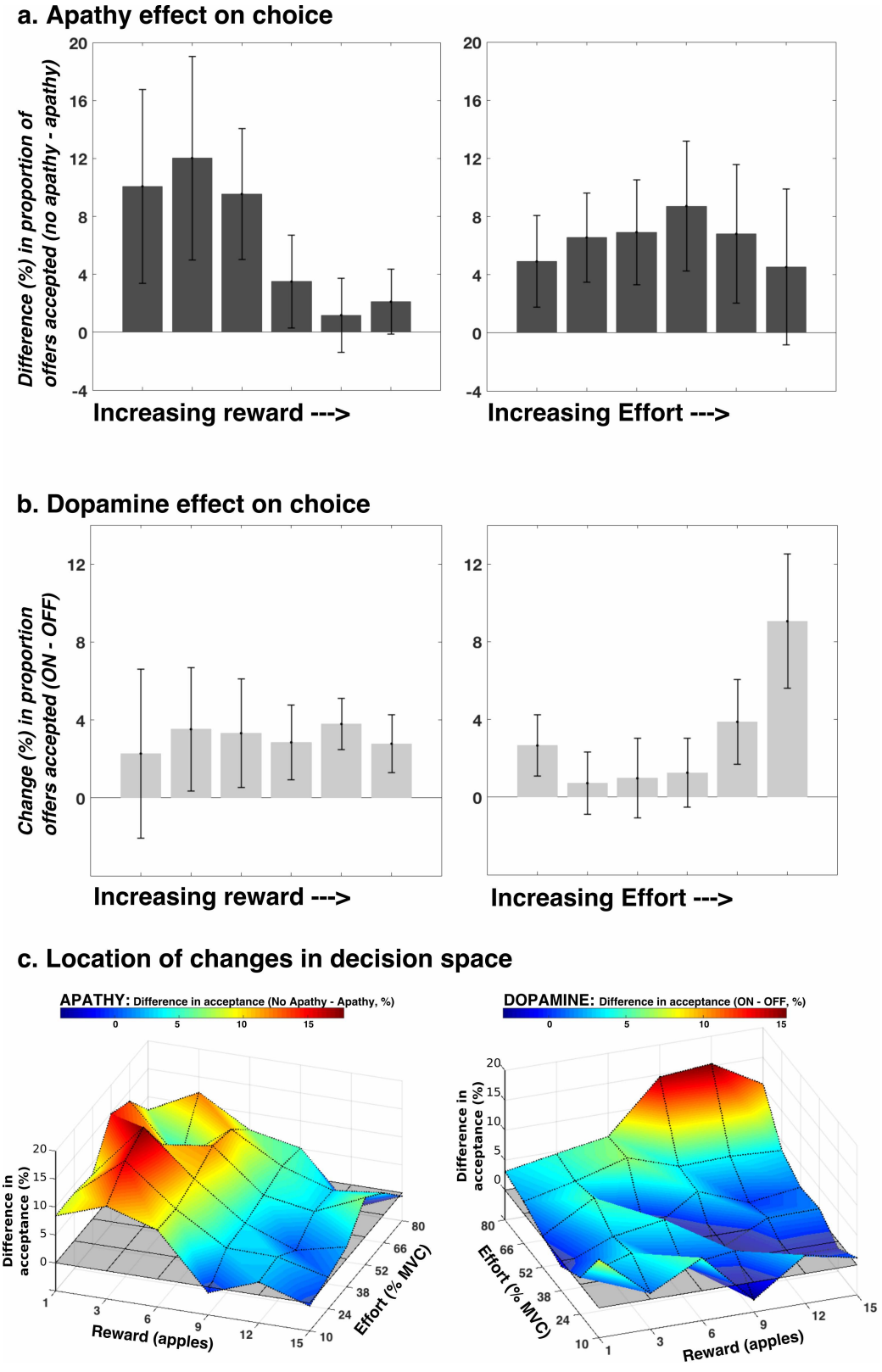


Figure 4-4. Distinct effects of apathy and dopamine depletion on response pattern

(**a**) Change in acceptance in apathetic compared to non-apathetic patients, as both reward and effort increase. The panels show difference in responding (% accepted in no apathy group minus % accepted in apathy group) at each reward level, collapsed across effort (**left panel**) and effort level, collapsed across reward (**right panel**). The

reduced acceptance rate seen in apathetic patients was driven by reduced responding to low reward offers, particularly when effort costs were lower (apathy*reward*effort interaction p=0.004).
(**b**) A different behavioural pattern characterised the effects of dopamine depletion (OFF state) on choice. Panels show the mean change in acceptance (ON minus OFF) across patients, as reward (**left panel**) and effort (**right panel**) increases. The difference between ON and OFF states was driven by increased responding to predominantly high effort, higher reward offers (dopamine*reward*effort interaction p=0.003).
(**c**) These differences in acceptance rates associated with apathy (**left panel**) and dopamine depletion (**right panel**) manifest within distinct regions of the 6x6 decision space grid. The grey shaded plane (z axis=0) represents no difference in acceptance. *All errorbars are +/- SEM.*

Table 4-2. Parameter estimates for the Full Model

Variable	Parameter Estimate	SE	T statistic	F statistic	P value
Intercept	2.72	0.28	9.89	97.9	<0.0001
Reward	2.40	0.056	43	1849	<0.0001
Effort	-1.29	0.049	-26.4	701	<0.0001
Apathy	-0.41	0.28	-1.49	2.23	0.14
Dopamine	-0.17	0.051	-3.38	11.44	0.0016
Session	0.14	0.029	4.79	22.95	<0.0001
Rew*Eff	-0.35	0.046	-7.89	62.3	<0.0001
Rew*Ap	0.03	0.056	0.48	0.23	0.63
Rew*DA	-0.08	0.050	-1.57	2.46	0.12
Eff*Ap	0.13	0.050	2.57	6.58	0.014
Eff*DA	-0.14	0.047	-2.87	8.24	0.0066
Ap*DA	0.03	0.053	0.61	0.37	0.55
Ap*Rew*Eff	0.14	0.046	3.02	9.15	0.0044
DA*Rew*Eff	-0.14	0.045	-3.13	9.84	0.0032
Ap*DA*Eff	0.08	0.048	1.76	3.09	0.087
Ap*DA*Rew	0.02	0.051	0.32	0.10	0.75
Ap*DA*Rew*Eff	0.05	0.046	1.11	1.23	0.27

4.4.3 Dopamine depletion, but not apathy, reduces raw motor response for reward

Dopamine increased the peak squeeze force each patient exerted to obtain rewards, *even though this increased output above the required force level was not coupled to any increase in reward* (mean increase in peak force = 2.5% of subject's MVC, SEM 0.72%, t(38)=3.47, p = 0.0013). This main effect of Dopamine (F(1,31) = 9.25, p = 0.005), was present for *both* high and low effort levels, with no interaction between effort and dopamine (F(5,155) = 1.4, p=0.24). Importantly, this effect of dopamine was *not* modulated by apathy status (Apathy * Dopamine effect F(1,31) = 0.68, p=0.42), nor was there a main effect of apathy on force exerted at each effort level (F(1,31) = 0.25, p=0.62). Thus once apathetic patients had accepted an option, their subsequent peak motor response was no different to non-apathetic patients (**Figure 4-5a**).

The subjective rating of the physical demand associated with each effort level did not differ between ON and OFF dopaminergic states, or between patients and controls (one-way ANOVA for group effect: F(2,95)=0.6, p=0.56; **Figure 4-5b)**. Additionally, apathetic people did not perceive effort as more demanding (**Figure 4-5c**). Of note there was no significant change in MVC between ON and OFF states: mean for right hand (ON vs OFF = 277.9 N vs 278.8 N; t(38)=-0.12, p = 0.9); left hand (234.1 N vs 234.8 N; t(38)=-0.07, p = 0.94; p values on paired t-tests; **Figure 4-5d**).

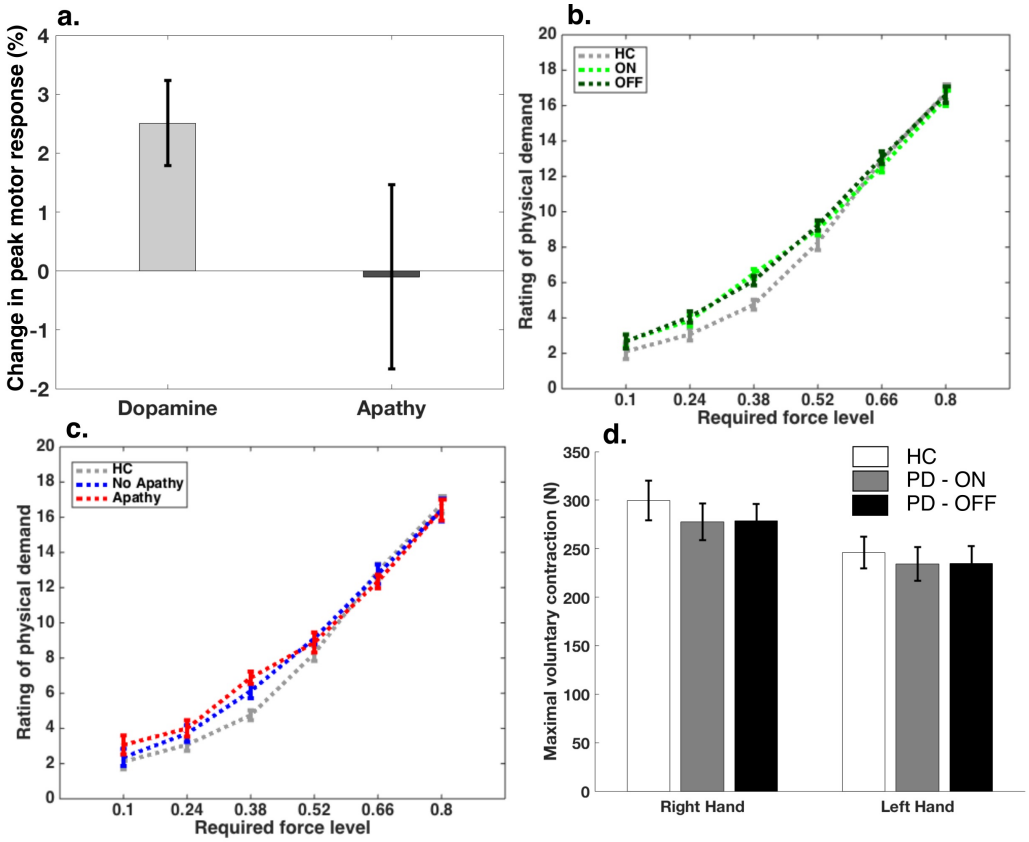


Figure 4-5. Dopamine depletion, but not apathy, reduces motor vigour following decision to engage.

(**a**) Motor vigour was indexed by *excess* force generated above the required effort level, i.e. how much more than was required that a participant squeezed. Dopamine (ON state) significantly increased response vigour (indexed by OFF state), whilst the presence of apathy was not associated with a significant change in the vigour of response. (**b**) Despite greater force production at each effort level in the ON state, there was no change in perceived physical exertion between ON and OFF state. (**c**) Similarly controls, apathetic and non-apathetic patients did not perceive the physical exertion differently. (**d**) Maximal voluntary contraction did not differ between ON and OFF states for either hand.

4.4.4 Decision time

Apathetic patients took on average 1.67s to make each decision (accept or reject an offer), compared to 1.49s for non-apathetic patients, although this difference was not statistically significant (p=0.35). Patients in the OFF state trended towards faster decisions than when in the ON state – mean(ON) = 1.67s, mean(OFF) = 1.48s, $F(1,37)=4.04$, $p=0.052$. There were also significant main effects of both reward ($F(3.4,125)=10.3$, $p<0.001$) and effort ($F(2.9,109)=7.9$, $p<0.001$) on decision time.

There was no interaction between apathy and dopamine, nor between these and the other terms (**Figure 4-6**). There was no relationship between decision time and UPDRS motor score (ON): R=0.17, N=39, p=0.30.

Decision time was also strongly related to offer value (reward discounted by effort) for both apathetic and non-apathetic patients, and in ON and OFF states suggesting all groups attended appropriately to the task (**Figure 4-7**).

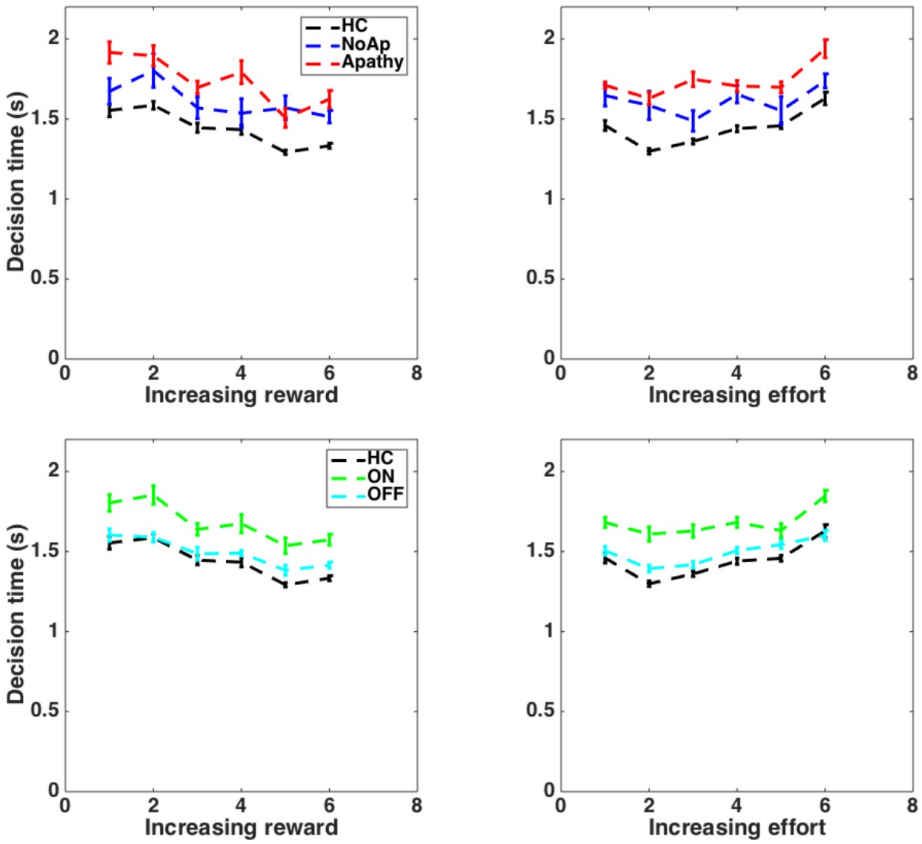


Figure 4-6. Decision time, apathy and dopamine

The mean decision time in the apathetic group was 1.67s, compared to 1.49s in the non-apathetic group, however this difference was not statistically significant (**Top Panels)**. Patients OFF their dopaminergic medications trended towards making *faster* decisions compared to ON (**Bottom Panels**).

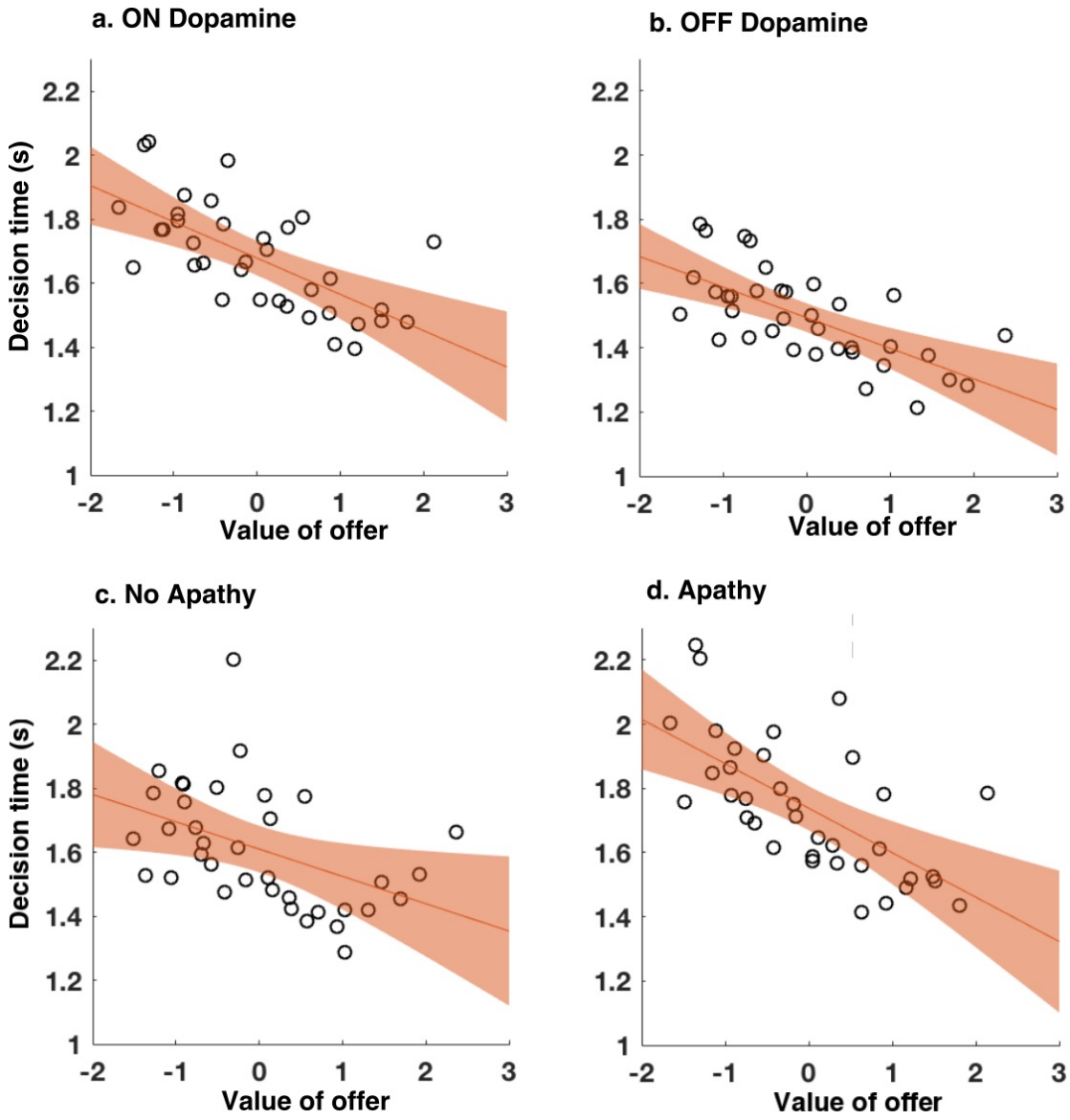


Figure 4-7. Relationship between decision time and offer value in each group

Decision time (time to accept or reject an offer) varied across decision space. Value of each reward/effort combination^ (36 in total) is plotted against average decision time ON and OFF dopamine, and with and without apathy. As value of an offer increased, decision time decreased, in both the ON and OFF states ($r^2 = 0.45$, $p < 0.0001$; $r^2 = 0.46$, $p< 0.0001$, respectively, **a & b**.), and for non apathetic and apathetic patients ($r^2 = 0.2$, $p=0.006$; $r^2 = 0.43$, $p<0.0001$, respectively, **c & d**.)

^(reward discounted by effort, computed using the parameter estimates of the fixed effects from the generalised linear model used in the primary analysis)

4.4.5 Additional analyses

Participants in both control and PD groups parametrically adjusted their force production to trial requirements (**Figure 4-1f**). Of note, participants achieved the force

requirements on the offers they accepted >95% of the time, and this did not differ between apathetic and non-apathetic patients ($t(37) = -1.19$, $p = 0.24$) or the ON and OFF states ($t(38) = -0.39$, $p=0.7$; **Appendix 3).** Their choices did not systematically change across the experiment, with no effect of block number on choice in the ON state ($F(4,179) = 0.03$, $p=0.99$), OFF state ($F(4,179) = 0.2$, $p=0.94$), or for apathetic ($F(4,179) = 0.11$, $p=0.99$) and non-apathetic groups ($F(4,179) = 0.04$, $p=0.98$; (**Appendix 3).** There was also no significant change in motor vigour between the beginning and end of the experiment (mean difference between 1st and 5th blocks = 0.008, p=0.21). Although vigour varied within the experiment, increasing during the first half of the experiment before returning towards baseline by the end, there was no drug*block interaction ($F(3.1,118)=0.98$, $p=0.41$; **Appendix 3**). There was also no relationship between change in UPDRS motor score and change in acceptance rate, ON and OFF dopamine ($R=0.15$, $N=39$, $p=0.35$).

Willingness to accept offers was not affected by the presence of dysphoria (assessed using the dysphoria subscale of the BDI-II) – proportion of offers accepted in low dysphoria group = 0.75 (+/- 0.028); high dysphoria group = 0.76 (+/- 0.04), $t(34) = 0.29$, $p = 0.77$ (**Appendix 3**).

Having Parkinson's disease was associated with a lower quality of life compared to healthy controls, however this change was entirely driven by a reduced quality of life in the apathetic group (Overall group effect: $F(2,65)=11.4$, $p<0.001$; PD-A vs PD-NA: MD=1.5, p=0.008, PD-A vs HC: MD=2.0, $p<0.001$ PD-NA vs HC: MD=0.5, p=0.58; **Table 4-1**).

4.5 Discussion

This study demonstrates that altered effort-based decision making is associated with the clinical phenotype of apathy in patients with PD. The effect is not a generalised reduction in willingness to engage in effort, but rather predominantly driven by reduced responding to *low reward* outcomes, suggesting apathy is associated with *reduced incentivisation by reward*, rather than increased sensitivity to action costs. This finding provides a plausible mechanism for the reduced goal directed behaviour

that characterises the apathetic state, and is strikingly similar to the changes in decision making associated with apathy in CADASIL patients. Additionally, the results demonstrate that although dopamine depletion also impacts upon effort-based decision making, it does so in a distinctly different manner to apathy, affecting individuals' willingness to accept predominantly *high effort*, *high reward offers*.

Whilst apathy has long been conceptualised as a disorder of goal directed behaviour (Levy and Dubois, 2006; Marin, 1991), empirical evidence based on neurobiological accounts of this is sparse (but see Le Bouc et al., 2016). The similarity of the apathy phenotype, across a diverse range of underlying pathologies, suggests a common neurocognitive system may be implicated in its aetiology. The brain network underlying effort-based decision making is one such candidate system intrinsic to normal motivated behaviour, and indeed a recent neurocognitive framework of apathy emphasises three core components of it that could potentially underlie the apathetic phenotype (Le Heron et al., 2017). They include: (i) deciding whether to act, (ii) persisting with an action, and (iii) learning about the outcome of an action, and are considered to be instantiated within brain regions implicated in PD apathy (Baggio et al., 2015; Carriere et al., 2014; Robert et al., 2014), particularly ventral striatum and dorsal anterior cingulate cortex (Hauber and Sommer, 2009; Kolling et al., 2016; Salamone et al., 2016). Here I provide empirical evidence implicating the first of these component processes – deciding whether to act – in PD apathy.

Importantly, this reduced responding is not global, but rather is limited to a subset of offers – those in which rewarding outcomes of actions are low (particularly when costs are low as well). Put another way, apathetic patients were prepared to exert effort – even high levels of effort – to the same degree as non-apathetic patients, *if the rewarding outcome was high enough.* In fact, apathetic patients showed reduced, rather than increased, effort sensitivity, despite modulating their force output in the same way as non-apathetic patients. These results are consistent with the hypothesis that PD apathy is associated with reduced incentivisation by the rewarding outcomes of actions, rather than an increased sensitivity to effort costs per se. They also mirror the changes associated with apathy in CADASIL patients performing the same task (Chapter TWO). As discussed in chapter TWO, these observations are consistent with evidence that physiological responses to reward are reduced in PD apathy (Lawrence et

al., 2011; Martinez-Horta et al., 2014a; Muhammed et al., 2016). These reward related signals are likely crucial for motivating behaviour towards a goal, overcoming the costs of action as an individual decides whether or not to act (Holroyd and Yeung, 2012; Rushworth et al., 2012; Salamone and Correa, 2012). More generally, this conceptualisation suggests that the core feature of clinical apathy – reduced goal directed behaviours – may manifest because patients no longer derive sufficient 'drive' from the outcomes of options in their everyday environment.

Effort based decision making was also affected by dopamine depletion. Specifically, the reduced responding observed in the OFF state was driven by greater rejection of offers *with higher associated effort costs and rewards*. This finding is consistent with recent animal research that suggests a crucial role for mesolimbic dopamine in overcoming the costs of work, by signalling the value of actions towards a goal (Hamid et al., 2016; Howe et al., 2013; Syed et al., 2016). More generally, it demonstrates the inextricable linkage that exists between the dopaminergic system and (motivated) goal directed actions towards incentives. The result is concordant with previous work which has demonstrated that manipulation of the dopaminergic system reduces effortful behaviour for rewards in animals (Salamone et al., 2007) and humans (Chong et al., 2015; Le Bouc et al., 2016), but extends it in two important directions.

Firstly, it demonstrates dopamine's effect on effort based decision making is present *across underlying motivational states.* Both apathetic and non-apathetic PD patients showed increased acceptance of high effort, high reward offers when ON compared to OFF their usual dopaminergic medications. Secondly, it demonstrates that dopamine depletion and apathy have dissociable effects on effort-based decision making. The common occurrence of apathy in conditions such as PD – in which a hypo-dopaminergic state is a defining feature (Aarsland et al., 2009; Kalia and Lang, 2015) – as well as neuroimaging work in PD patients who have developed apathy in the context of deep brain stimulation (Thobois et al., 2010) and de novo (Santangelo et al., 2015) has led to the hypothesis that apathy in PD occurs as the result of a dopaminergic denervation within the mesolimbic system (Thobois et al., 2010). This has motivated therapeutic trials to treat apathy in PD with further dopamine replacement. However, as outlined previously results have been mixed (**Chapter 1**).

These results, in which apathy and dopamine (depletion) were associated with dissociable changes in the pattern of responding in an effort-based decision making task, suggest distinct mechanisms may underlie their effect on motivated behaviour. This is concordant with a recent study that assessed the effects of apathy and dopamine on autonomic responses (change in pupillary dilatation) to reward. Apathetic patients showed a reduced autonomic response to reward (in the same fashion as the apathetic CADASIL patients), and although dopamine increased the magnitude of this response, it did so in *both* apathetic and non-apathetic groups, such that there was no drug by apathy interaction (Muhammed et al., 2016). Similarly, in the current study although dopamine administration was associated with increased acceptance of offers in apathetic (and non-apathetic) patients, it *did not change the underlying apathetic pattern of responding* – that is a failure of *low rewards* to incentivise behaviour. Together, this suggests a general invigorating effect of dopamine across underlying motivational states, but along a separate mechanistic axis to that underlying apathy.

Apathy and dopamine also showed dissociable effects on response vigour, assessed by the peak motor response at each required effort level. Strong evidence from animal work suggests the dopaminergic system plays a crucial role in appetitive, activational behaviour – that is modulating vigour and persistence of action(s) towards a goal (Salamone and Correa, 2012). A recent computational account of dopamine's effects on choice and response revealed an independent effect on motor activation rate, speeding up the rise of force (yank) to its peak (Le Bouc et al., 2016). In the present study, dopamine depletion reduced peak motor response (for reward) in PD patients, independent of reward on offer. Importantly there was no change in the maximal force a subject could produce (MVC) between the two conditions. Interestingly, despite patients exerting more force ON than OFF medications, their perception of how physically demanding the effort was did not change. The same effect was not observed for apathy: whilst apathetic patients showed reduced engagement with offers, once an offer was accepted apathy had no effect on the vigour of the squeeze. Additionally, there was no interaction between apathy and the effect of dopamine on response vigour; as with choice, dopamine exerted its effect whether patients were apathetic or not. The findings reported here regarding the effects of dopamine are in line with Le Bouc et al, but use a different analysis approach, whilst also demonstrating that this

effect is general (present across decision space) and independent of the presence of clinical apathy.

The results demonstrate effort-based decision making is disrupted in PD apathy, but in a manner distinct to that associated with dopamine depletion. This does not rule out a role for disruption of dopaminergic systems in the aetiology of apathy, but suggests this alone may not be sufficient to explain the development of the syndrome, nor should it be the sole focus for therapeutic interventions. This conclusion would be consistent with recent reviews of the neurobiology of motivated behaviour and decision making, which also emphasize the importance of non-dopaminergic neuromodulators (Bailey et al., 2016a; Salamone et al., 2016). These include serotonin (Bailey et al., 2016b; Maillet et al., 2016), acetylcholine (Fobbs and Mizumori, 2014), noradrenaline (Varazzani et al., 2015) and adenosine (Nunes et al., 2013). Indeed, manipulations of these systems have also shown some promise for the treatment of apathy in other conditions (Callegari et al., 2016; Rea et al., 2015). The heterogeneity in the effects of the dopamine manipulation on choice responses was also a notable feature of this study. An open question is whether those apathetic subjects in whom dopamine depletion had a greater effect on choice would be more likely to attain a therapeutic benefit from (increased) dopaminergic treatment for their apathy.

As in the CADASIL study, performance on the effort-based decision making task correlated with the action initiation subscale of the LARS, consistent with previous work in healthy people (Bonnelle et al., 2016). The lack of correlation with other LARS subscales could suggest that disruption of effort-based decision making mechanisms is just one mechanism by which apathy can develop. Indeed impairment of executive functions such as planning have also been associated with apathy in PD (Weintraub et al., 2005), whilst a recent review emphasises, in addition to the above factors, the potential contributions of emotional distress (Pagonabarraga et al., 2015). However, it still remains unclear how the different questionnaire components relate to underlying neurobiological systems, the dysfunction of which must drive the development of apathy. As discussed earlier, an alternative approach to investigating the underlying mechanisms of apathy is to start from implicated cognitive systems (for example effort-based decision making) and work upwards, testing which components are associated with the clinical syndrome of loss of motivation (Holroyd and

Umemoto, 2016; Le Heron et al., 2017; Salamone et al., 2016). Future work might profitably focus on whether other neurally dissociable factors of motivated behaviour – such as persistence towards a goal (Hamid et al., 2016; Holroyd and Yeung, 2012; Howe et al., 2013), tracking of background environmental reward information to compare the value of current and alternative actions (Pearson et al., 2014) and learning from the outcomes of actions (Hauser et al., 2017; Holroyd and McClure, 2015; Scholl et al., 2015) – are also disrupted in apathy, and whether dopamine plays a modulating role. Furthermore, whilst this study provides behavioural evidence that disrupted decision making underlies apathy in PD, future work should focus on linking these behavioural changes to the neural substrates that underlie normal effort-based decision making (in a manner similar to Chapter THREE). These regions, including anterior cingulate cortex and ventral striatum, have already been associated with PD apathy in separate imaging studies (Baggio et al., 2015; Carriere et al., 2014; Remy et al., 2005) but it would be an important next step to link these changes to specific, measurable behavioural changes.

In this study the presence of apathy was associated with reduced quality of life. The last two decades have seen a surge in recognition of the importance and impact of non-motor features of Parkinson's disease (Aarsland et al., 2009; Chaudhuri et al., 2006). A recent study demonstrated that, following deep brain stimulation treatment for motor symptoms, those without apathy at baseline experienced a significant improvement in quality of life, whilst those with apathy did not, despite showing the same degree of improvement in motor symptoms (Martinez-Fernandez et al., 2016). The current study adds further evidence that apathy is an important factor in a patient's global well-being, reinforcing the importance of understanding its mechanisms and developing effective treatments.

In interpreting these results, it is worth considering strengths and potential limitations of this study. The findings suggest that dopamine has a dissociable effect from apathy on effort based decision making. However, the dopamine manipulation was within the context of PD, itself a hypo-dopaminergic condition. This means that even ON dopamine, it is very unlikely patients had normal function within dopaminergic pathways. Additionally, although I conclude that depleting dopamine produces an effect distinct to apathy on effort based decision making, I cannot speculate as to

whether a supra-therapeutic level of dopamine might in fact have altered the reduced incentivisation by low reward outcomes that characterised apathy. It is also important to note that degeneration of the mesolimbic dopaminergic system (and particularly structures such as ventral striatum) has been associated with the development of PD apathy (Remy et al., 2005; Santangelo et al., 2015; Thobois et al., 2010). These changes in themselves may limit the effect of further dopamine administration on the apathetic state. The study included a number of patients with relatively mild motor symptoms, who consequently were not requiring high doses of dopaminergic medications. This meant the overall magnitude of dopamine manipulation was not as high as some previous studies (e.g. Le Bouc et al., 2016). However the fact I was able to demonstrate robust effects of dopamine on different components of effort based decision making suggests this was not a significant issue. There is also always the possibility of a confounding factor influencing apathetic performance on the task (for example reduced attention). However, the observation that apathetic subjects modulated effort output appropriately, showed specific rather than global alterations in choice behaviour, and demonstrated the same changes in decision time to the value of offers as non-apathetic subjects, makes this unlikely in my opinion. Additionally, the study design controlled for potentially confounding factors on choice such as temporal delay (there was the same delay until the next trial whether an option was accepted or refused) and fatigue, and baseline levodopa equivalent dose was similar between the groups. Although apathetic PD patients had a higher level of total depressive symptoms, they did not differ from non-apathetic patients in levels of dysphoria symptoms. Furthermore, and consistent with the conceptualisation of apathy and depression as dissociable constructs, dysphoria was not associated with changes in effort-based decision making. The patient population was drawn from a number of local PD clinics, and thus is likely to be generally representative of the spectrum of PD likely to be seen in other general neurology populations.

This study demonstrates specific but distinct effects of apathy and dopamine on effort-based decision making during both decision and response phases. Apathetic patients showed reduced incentivisation by rewarding outcomes, and whilst dopamine increased their responding, it did not change this underlying response profile. More broadly it provides empirical evidence for a neurobiological substrate to explain the reduced goal directed behaviour that characterises apathy – disrupted effort based

decision making – building on the evidence from the CADASIL study. It also suggests that the motivational deficit seen in PD is not simply secondary to dopaminergic depletion of mesocorticolimbic pathways, but is better construed as a more complex phenomenon that may encompass both anatomical changes and other neuromodulatory systems.

5 Chapter 5 – An ecological framework for effort-based decision making

5.1 Chapter Summary

Foraging theories of decision making emphasise a comparison between foreground and background reward contexts, explain animal behaviour in naturalistic and experimental settings, and neurally may be instantiated within the same brain regions in which damage is associated with apathy in humans. However, it has not been convincingly demonstrated that human decision makers are sensitive to the predictions of the marginal value theorem (MVT), and nor do appropriate tasks exist in which to do this. In this chapter I use a novel patch leaving paradigm to investigate, over a series of experiments, how healthy human decision makers adjust behaviour to the different variables specified within the MVT. I then examine whether apathetic traits in this healthy population are associated with changes in sensitivity to these variables. The results demonstrate that human decision makers adjust their behaviour when performing a patch-leaving task in a manner closely described by optimal foraging theory, and that sensitivity to the background reward environment is associated with higher levels of apathetic traits.

5.2 Introduction

In the previous three chapters, I have presented evidence that effort-based decision making is altered in patients with apathy. Specifically, it seems apathetic patients are not as incentivised by the rewarding outcomes of their actions, manifesting in reduced goal directed behaviour. Although the paradigm used in these studies has proved very useful for dissociating the effects of reward and effort on choice, it treated each decision point (accept/reject) as independent from all others – i.e. *the experiment was a series of single decisions* in which participants evaluated what was right in front of them, in isolation. Real-world decision-makers however must evaluate options within their *current environmental context.* Decisions are not always between option "a" and

option “b”, but rather a choice between foreground – *what am I doing right now* – and background – *what else could I be doing*. These types of decisions are often called foraging decisions after the ecological behaviours they describe, and it is likely that animal brains have evolved within an environment where optimising solutions to these problems has a distinct survival advantage (Geoffrey K. Adams et al., 2012; Pearson et al., 2014). Indeed there is now a wealth of evidence in the behavioural ecology literature that animals behave according to the predictions of models of this foreground-background approach (Geoffrey K Adams et al., 2012; Cassini et al., 1990; Charnov, 1976; Cuthil et al., 1994; Krebs et al., 1977; Munger, n.d.; Nonacs, 2001; Pyke, 1978; Ydenberg, 1984). There is also accumulating evidence, in both humans and animals, that brain regions associated with effort-based decision making, and apathy, encode these same variables to drive behaviour (Hayden et al., 2011; Kolling et al., 2012; Le Heron et al., 2017; Rushworth et al., 2012). This has led some authors to consider that foraging decisions may provide an ecological framework within which the computations associated with effort-based decision making are instantiated (Kolling et al., 2016; Pearson et al., 2014). Disruption of this class of decisions may also underlie neurobehavioural syndromes such as apathy (Le Heron et al., 2017).

However, surprisingly little is known about whether healthy human decision-makers adhere to the predictions of foraging models of behaviour – in part because the majority of human decision making experiments have not emphasised a foreground/background design (Hayden and Walton, 2014). A key foraging question that has been extensively studied in the animal ecology literature is the so-called patch leaving problem (Nonacs, 2001; Stephens, 2008; Stephens and Krebs, 1986). Simply, animals often harvest rewards from one location (a *patch*, e.g. a bumble-bee in a flower), but the rate of return at this location drops as rewards are depleted over time. At any point the forager can choose to leave the current patch, however this leaving decision incurs costs of time and effort (to reach the next patch). So when should a forager leave their current patch? The MVT provides a mathematical solution to this problem (**Figure 1-5**). It demonstrates that foragers optimise their long-term energy intake by leaving each patch when the foreground reward rate (instantaneous reward rate in the current patch) drops below the environment background reward rate (Charnov, 1976; Stephens and Krebs, 1986). A plethora of studies involving animals from across the kingdom have now demonstrated that behaviour can be modelled *as if*

these animals are tracking the variables central to the MVT (Charnov, 1976; Krebs et al., 1977; Nonacs, 2001; Pyke, 1978; Stephens et al., 2007; Stephens and Krebs, 1986). However only a few studies have examined this problem in humans, and results have been discordant. Whilst a recent study specifically modelling learning in a patch leaving decision making task concluded that foraging models best accounted for observed behaviour (Constantino and Daw, 2015), an earlier study concluded that simple heuristics (e.g. leave after a certain number of trials) better explained human behaviour (Hutchinson et al., 2008). A number of anthropological studies have suggested that human hunter-gather behaviour follows the predictions of the MVT (Aswani, 1998; Metcalfe and Barlow, 1992; Smith et al., 1983), although it has been noted these observations represent qualitative, rather than quantitative evidence for human foraging behaviour (Hutchinson et al., 2008). Therefore, it remains unclear whether optimal foraging theory provides an accurate account of human decision making behaviour, and no research has systematically investigated how the different parameters of MVT impact on cost-benefit decision making.

Still less is known about the relationship between apathy and foreground/background decision making. Intriguingly, brain regions in which damage is associated with apathy are the same regions in which foraging decisions seem to be instantiated (Hayden et al., 2011; Kolling et al., 2012; Le Heron et al., 2017). Furthermore apathy has been associated with altered processing of reward information (Martinez-Horta et al., 2014a; Muhammed et al., 2016; Rochat et al., 2013; Schmidt et al., 2008), and in a recent study the failure of rewards to incentive behaviour was associated with the apathetic phenotype (Le Heron et al., 2018). However it is unclear how these findings translate to a situation in which foreground and background reward information is represented separately, and furthermore must be integrated to drive behaviour – the core process thought to underlie patch leaving (Hayden et al., 2011). Nonetheless, this central foraging decision variable relies on integration and comparison of rewards and costs – a process which appears to be disrupted in apathetic patients (**Chapters 2, 3 & 4**). Is the reduction in goal-directed behaviour associated with apathy caused by a failure to patch leave – to shift from the current activity to another (even if the current activity is minimal)? And could this be driven by underestimation of background environmental reward rates? Or more generally a failure to generate switching behaviour due to damage to crucial brain regions like ACC? In order to effectively investigate these

(and related) questions, it is paramount to establish that healthy human behaviour is indeed sensitive to the predictions of the MVT. In this chapter I present a series of experiments in which I test whether the behaviour of healthy participants conforms to the predictions of optimal foraging theory, using a novel patch leaving paradigm. Furthermore, I investigate whether variation in sensitivity to the different MVT parameters is associated with the presence of apathetic traits.

5.3 General methods

5.3.1 Participants and ethics

All participants were healthy volunteers, free from any significant neurological conditions and recruited via local databases. Specific demographics are listed for each study population below. Participants were paid a minimum amount for participation, which could be increased based on task performance. This total varied between £8-16 for experiments 1-3, and £35-45 for experiment four (which also included an imaging component). Baseline measures of apathy traits were collected using the self-rated apathy motivation index (AMI) (Ang et al., 2017).

This study was approved by the local ethics committee and written consent was obtained from all subjects in accordance with the Declaration of Helsinki.

5.3.2 Decision making task

I designed a computer-based patch-leaving task, in which participants aimed to maximise their overall return (and therefore money earned) based on reward and cost characteristics (**Figure 5-1, Figure 5-4, Figure 5-6 and Figure 5-8**). For experiments one, two and three participants were seated in front of a desktop computer running PsychToolBox, implemented in MATLAB (Mathworks, USA), and registered their responses using the keyboard. Experiment four was part of an fMRI study, and responses were registered with a hand-held button box from within the scanner. Only the behavioural component of this study is presented here.

To improve participant engagement, the task was framed in a "real-world" (farm-yard) setting, and payments made contingent on performance. The participants' goal was to collect as much milk as possible from fields of cows, which were located on farms. Participants chose how long to remain in fields (patches) in which they automatically accumulated milk at an exponentially decreasing rate. Moving on from a field was associated with a delay cost (as they 'walked' to the next field) during which time they could not collect any milk, and sometimes a physical effort cost ('climbing a fence to reach the next field'). The fields were grouped on a farm – participants had only a limited amount of time on each farm, but a theoretically unlimited number of fields were available. Therefore each farm had a background 'environmental' reward rate, determined by costs to move between fields and the yield of these fields.

On each trial, participants had to decide *when to leave* their current field to move to the next one. Milk collected in the current trial was displayed on the screen as a white bar continuously filling up a grey bucket – which filled up slower and slower over time. Therefore the longer they spent in a given field, the more milk they would receive, but the lower their instantaneous rate of return would be. They left each field by releasing the spacebar (experiments 1-3) or pressing a button on a hand-held button box (experiment four). When participants arrived at the next field the bucket would appear empty, but immediately start filling up with milk at a rate determined by the patch gain function – this starting rate was much higher than the typical and optimal leaving times. In the experiments where different patch-types were used (three and four) participants were aware of the background distribution of the patches, but could only work out the current quality of the patch by watching the bucket fill. Costs to move onto the next field were displayed continuously whilst the participant was in a field – a circle coloured to indicate the length of time before reaching the next field, and where applicable (experiments two and four) a bar coloured to indicate how hard they would have to squeeze on a hand-held dynamometer.

Participants were aware there were an unlimited number of fields available on each farm, but only a limited amount of time. They had approximate knowledge of the time they would spend (e.g. *"around 7 minutes")*, but no cues to indicate how long they had been in a given farm. They were instructed to decide how long to stay in each field,

such that they maximised their overall milk gain across the whole experiment. Each farm formed a separate, independent block, and the number of farms in an experiment varied depending on the variables being tested. Costs to move on (delay and effort) were blocked, such that on a given farm travel time between fields and any effort required would be the same. The variables that could be manipulated within this paradigm were:

1) Delay cost (transit time) to move to a new patch
2) Effort cost (physical) to move to a new patch
3) Reward characteristics of the current field – decay rate and scale
4) Background farm (environment) reward rate – by changing the distribution of high and low yield fields.

The foreground reward rate was determined by the patch gain function, an exponential function of the form:

$$\boldsymbol{g(T) = S * e^{-aT}}$$

Where S = the scale of the function; a = the decay rate; and T = time in patch

The background reward rate was determined by the average patch gain rate minus any effort costs associated with moving on, all divided by travel time costs plus average time spent in each patch type:

$$\boldsymbol{R_B = \frac{\sum p_i * g_i(T_i) - E}{d + \sum p_i * T_i}}$$

Where R_B = background reward rate; p_i = probability of being in the ith patch-type; $g_i(T_i)$ = gain function for the ith patch at leaving time 'T'; E = effort costs to move on; and d = travel time to the next patch.

For the case where there is only one patch-type (as in experiments one and two), this equation simplifies to:

$$\boldsymbol{R_B = \frac{g(T) - E}{d + T}}$$

From the marginal value theorem (**Figure 1-5)** the optimal time (T) to leave a patch is the time at which the instantaneous yield of milk g`(T) is equal to the background reward rate (R_B). (Charnov, 1976; Stephens and Krebs, 1986) **Figure 5-2**. In this experimental paradigm, we can therefore assess the effects of changes in the different variables on participant behaviour, and compare these effects to the mathematically optimal changes predicted by the MVT.

Before commencing the experiment, participants were trained on the task elements via a structured explanation and practice session lasting approximately 25 minutes in total. Comprehension of the different elements was checked before commencing the main experiment. Participants were *not* given any instructions on what optimal behaviour would be.

Rationale behind task design features

I used a *continuously changing* patch gain function rather than stepped changes as in previous human paradigms (Constantino and Daw, 2015; Hutchinson et al., 2008). This setup mirrors a number of real world situations (e.g. harvesting pollen from a flower, picking blackberries from a bush). It also reduces the chances of subjects reverting to a simple heuristic to drive behaviour (e.g. leave after 5 harvests), and has the statistical advantage of leaving the dependent variable (leaving time) close to normally distributed, as well as affording greater precision to the outcome variable of "when" participants leave. Finally, although not the focus of this thesis, this task will be used to examine changing neural signals associated with patch leaving behaviour over temporally extended periods, something which the continuous experimental design is better suited for.

Costs were blocked rather than interleaved, so that the effects of changes in these variables could be more easily demonstrated. In an interleaved design (e.g. where travel time varied from patch to patch on a given farm), an appropriate strategy would be to average across all delay costs to determine a single background reward rate, minimising the effect of the delay manipulation.

I chose to use an exponentially decreasing gain function, rather than for example a linear one. Rewards are less likely to decay linearly in ecological environments and

pilot testing of both functions favoured the exponential decay function, which produced a more engaging task. Furthermore milk flow rate from a dairy cow decays according to an approximately exponential function (Edwards et al., 2014).

The specific parameters for the different MVT variables were selected to ensure sufficient predicted effect sizes (from optimal foraging theory), whilst maximising the number of trials per experiment.

An underlying assumption of foraging theories is that foragers have complete information about their environment (Stephens and Krebs, 1986). Therefore in this task participants were explicitly cued to the relevant MVT variables.

5.3.3 General analysis methods

For experiments one, two and three I used a RM-ANOVA as the primary analysis method. For experiment four, which had a more complex structure, I estimated parameter effects for each subject using a general linear model. I also ran a mixed effects model for experiment four to test whether there were any higher order interactions.

Prior to formal analysis, raw data was inspected for evidence of obvious outliers, or other systematic issues. I used a cut-off level of 3 standard deviations above the mean group variance in decisions to exclude outliers from further analysis. I chose variance for the cut-off instead of raw leaving times as leaving times are effectively demeaned within each subject for all analyses.

For clarity, I present the specific methods and results for each experiment sequentially, before discussing all results in the final section of this chapter.

5.4 Experiment ONE – delay and patch leaving behaviour

Aim: To determine if human decision-makers are sensitive to changes in travel time between patches, and how this sensitivity relates to the predictions of optimal foraging theory.

5.4.1 Methods

Participants: Twenty (10/10 female/male, mean age 28, range 22-51) healthy volunteers were recruited via a local database. 2 participants were subsequently excluded because of not engaging with the task (1) or having false beliefs about the task (1).

Experimental variables (Figure 5-1):

- **Delay Costs:** 5, 10 and 20 seconds (block design)
- **Effort Costs (between patches):** nil
- **Patch-types:** Only one patch-type, S = 45; a = 0.075
- **Blocks:** There were 6 blocks, with participants visiting each farm-type twice in a pseudo-randomised order. Participants spent 6 minutes on each farm (moving on automatically following the transit period of the first leaving decision after 6 minutes had elapsed).
- **Key Press:** To test if the mechanism of patch leaving (pressing the spacebar vs holding it down then releasing it) affected patch leaving decisions, each subject completed 3 blocks of each of these conditions, in a pseudo-randomised order.

The background reward rates for each delay cost (and farm) were 21.1mL/s, 16.3mL/s and 11.7mL/s (for the 5, 10 and 20 second delays respectively), corresponding to predicted leaving times of 10.1s, 13.6s and 18s (**Figure 5-2**).

Statistical analysis

The primary analysis was conducted using a RM-ANOVA, with leaving time the dependent variable and travel cost a within subject predictor variable. A Greenhouse-

Geisser correction was applied because the assumption of sphericity was violated (Mauchly's test ε=0.643, p=0.002).

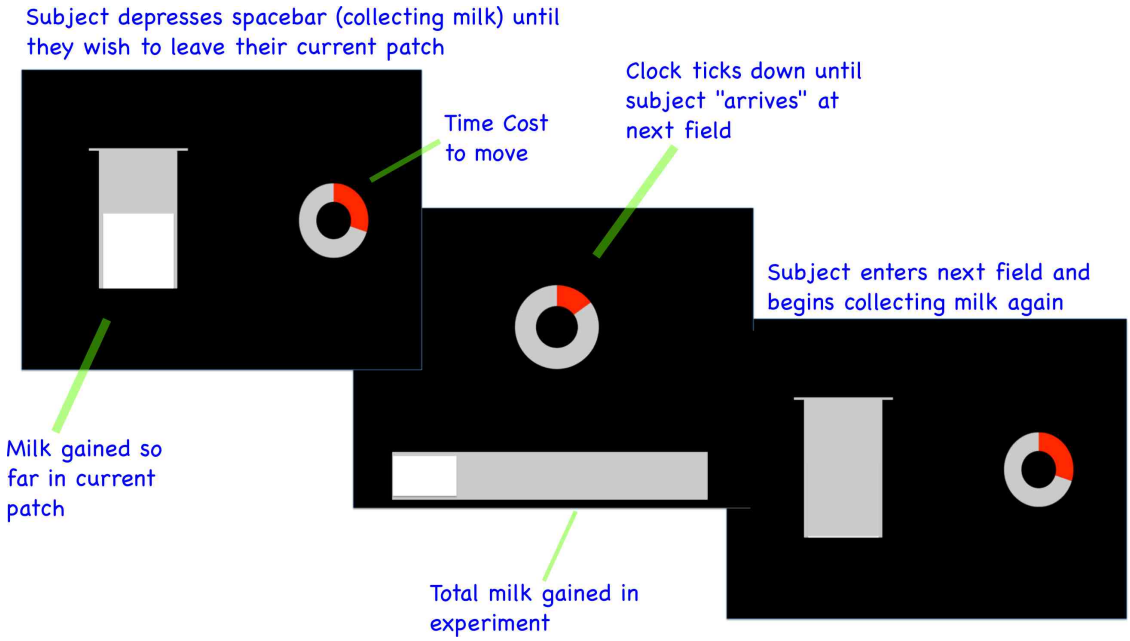


Figure 5-1. Delay paradigm

The grey bucket (left screen) continuously fills with milk (white bar), indicating how much milk has been collected in the current patch. The rate of filling reduces exponentially over time. To the right of the bucket the red portion of the circle indicates the time costs associated with moving onto the next patch. When the participant chooses to leave their current patch (by releasing the spacebar), they see the central screen, displaying the total milk earned so far in the experiment (bottom) and the time remaining until they reach the next patch. The right hand screen demonstrates the starting point of the next trial, as the participant enters the next patch (field).

5.4.2 Results

There was a main effect of delay cost on patch residency time, with participants leaving patches later when travel costs were longer: $F(1.3,21.9)=40.7$, $p<0.001$; mean difference: short vs medium = 4.5s, $t_{16}=5.4$, $p < 0.001$; medium vs long = 7.6s, $t_{16}=5.7$, $p<0.001$ (**Figure 5-3a & c**).

Participants also showed a bias to stay in patches longer than predicted by the MVT, for all three delay times. The mean deviation from predicted optima was: Short = 3.4s, $t_{17}=2.9$, p=0.01; Medium = 4.5s, $t_{17}=3.9$, p=0.001; Long = 7.7s, $t_{17}=3.9$, p=0.001

(**Figure 5-3a**). However *the magnitude of the effect of delay* was broadly consistent with optimal MVT predictions. The effect of delay on leaving time in participants for short and medium delay environments was not significantly different to optimal (mean difference +1.0s, t_{17}=1.3, p=0.22), although they did show greater sensitivity as delay costs increased (mean difference in delay effect for long-medium costs = 3.2s, t_{17}=2.4, p=0.03 **Figure 5-3b & c**). Overall, participants performed close to optimally on this task, with 16/18 accumulating more than 90% of available milk (**Figure 5-3d)**. Whether participants pressed or released a key to leave a patch did not have a significant effect on patch leaving time (F(1,17)=0.4, p=0.54).

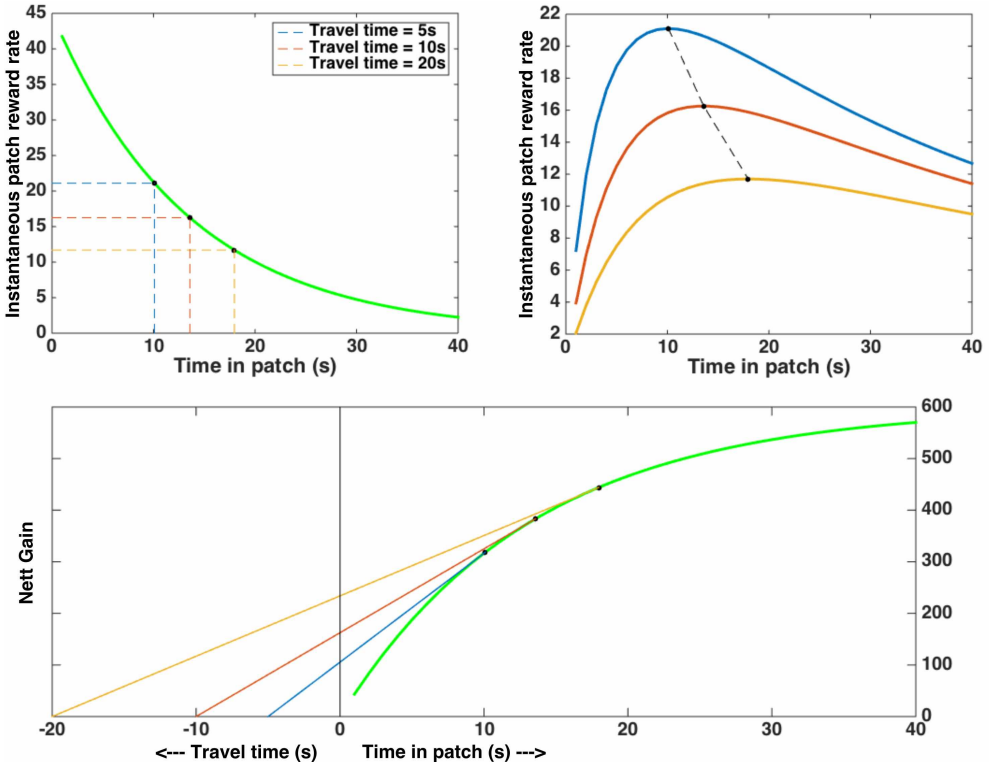


Figure 5-2. Optimal leaving times as travel time between patches changes

Milk yield in each patch reduced as time in patch increased, following an exponential decay function. Optimal patch leaving time occurred when the reward gained at time T was equal to the background average reward rate (**dotted lines, top left panel**). Longer travel times reduced the background reward rate and hence the optimal instantaneous patch reward rate to leave the current patch, increasing the predicted patch residency time (**top left panel**). As per the marginal value theorem, the time at which reward rate ($\frac{Gain}{travel\ T+patch\ T}$) peaks (and therefore the second derivative = 0) corresponds to the optimal patch leaving time (**top right**). For the unique situation where patches have equal properties (as in this experiment) and energetic costs are ignored, the tangent of the gain function at the optimal patch leaving time intersects the x-axis at the (negative) travel time (**bottom panel**).

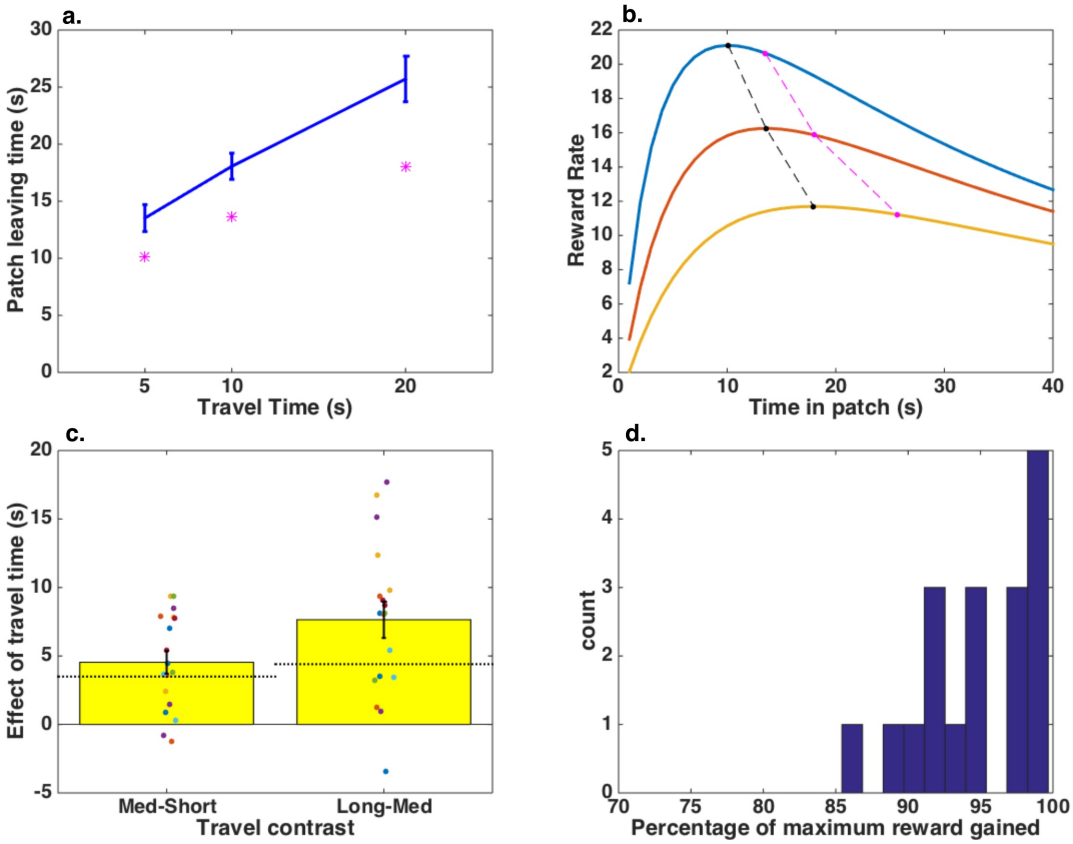


Figure 5-3. Patch residency time increases as a function of travel time

(**a & b**) Increasing travel time costs between patches was associated with increased patch residency time, and a lower patch reward rate at leaving time. The pink asterisks denote the optimal patch leaving time for each delay cost, and participants actual leaving times are shown by the blue line (**a**). For each delay cost (5, 10 and 20s shown as blue, red and yellow lines respectively) the optimal (black dotted line) and actual (pink dotted line) reward rates at leaving time are plotted (**b**). (**c**) By de-meaning leaving times within each participant, the magnitude of the effect of delay (for medium compared to short, and long compared to medium) conditions can be visualised. This effect was similar to the predictions of optimal foraging theories. (**d**) Overall most subjects performed close to optimally on this task.

5.4.3 Summary

The results demonstrate changes in patch leaving behaviour as delay costs (and therefore background reward rate) vary, refuting the null hypothesis that human decision makers are not sensitive to the predictions of MVT. Furthermore, although a baseline bias to remain in all patches for longer than predicted was present, participants performed at a level close to optimal, collecting most of the available reward.

5.5 Experiment TWO – effort costs and patch leaving behaviour

Aim: To determine if human decision-makers are sensitive to effort costs to move between patches.

5.5.1 Methods

Participants: Sixteen healthy volunteers (10/6 female/male, mean age 24, range 21-30) were recruited via a local database. 2 participants were subsequently excluded because they did not engage with the task.

Paradigm: In addition to the previously described experimental setup, participants held a dynamometer (SS25LA, BIOPAC Systems, USA) in their dominant hand. This was calibrated to each individual based on the highest force exerted across three maximum squeezes (maximal voluntary contraction – MVC), and used to exert physical effort when moving between patches.

During the travel period, participants were given a three second window during which they had to squeeze to exceed the required force for at least one second, with real-time feedback displayed by a red rectangle whose height corresponded to force exerted. The rectangle turned green whenever they were above the required force. If they failed to achieve the force level a message *"sorry, fence not climbed, please try again"* was displayed and they were given another opportunity (at a time cost of an additional 5 seconds). If they were still unsuccessful the message *"sorry fence not climbed, 10 second penalty"* was displayed, and they then waited an additional 10 seconds before moving onto the next field. The top force level was set at 60% of a participants' MVC.

Experimental variables (Figure 5-4):

- **Delay Cost:** 5 seconds
- **Effort Costs (between patches):** 0%, 30% or 60% of MVC (blocked)
- **Patch-types:** Only one patch-type, S = 45; a = 0.075
- **Blocks:** Six 180 second blocks, with participants visiting each farm-type twice in a pseudo-randomised order.

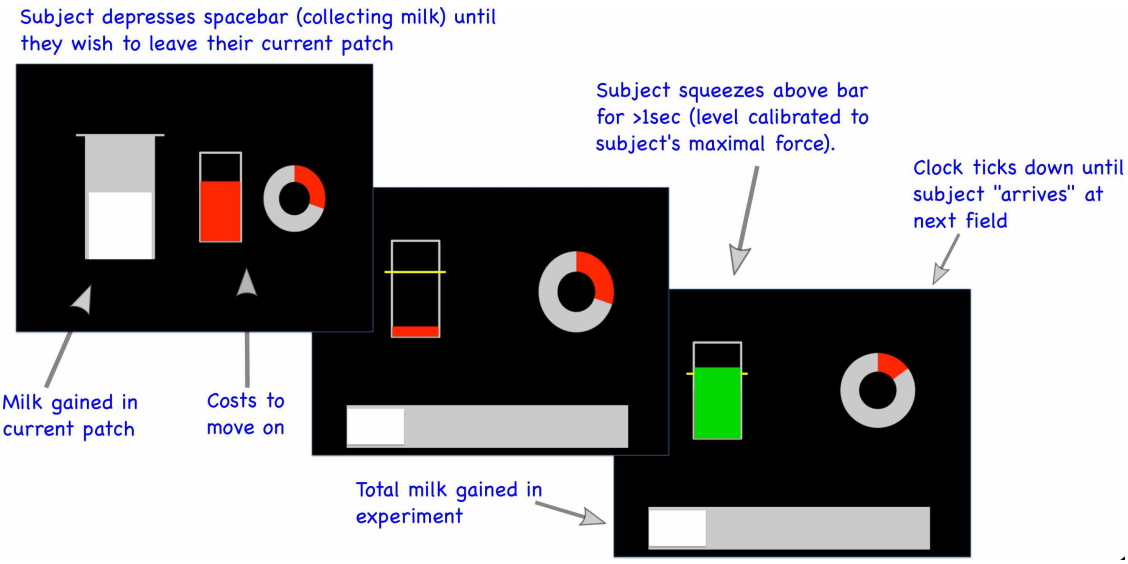


Figure 5-4. Effort paradigm

As with experiment one, participants were presented with a continuously increasing (but exponentially slowing) white bar, indicating the reward (milk) gained in their current patch thus far, as well as information about time costs to reach the next field (circle). Additionally, the effort costs to switch fields were also displayed, signalled within the patch as the proportion of the central rectangle coloured red. During the travel phase (central and right screens), participants squeezed the hand-held dynamometer (with real-time feedback), to a level greater than the yellow line – when achieved the red rectangle indicating force exerted changed to green – and held it here for at least one second.

Statistical analysis

The primary analysis was conducted using a RM-ANOVA with leaving time the dependent variable and effort cost predictor variable.

The subjective cost of effort (which, in contrast to delay, cannot be 'optimally' predicted) was inferred for each participant by multiplying the average patch reward rate on patch leaving in LOW effort environments (the presumed individual estimate of background reward rate) by the extra time spent in HIGH effort environments. After subtracting the increased yield associated with staying longer in a patch, this calculation returned the reward that participants gave up by remaining in the patch for longer in high effort conditions. (**Figure 5-5c**).

5.5.2 Results

There was a main effect of effort on patch leaving time, driven entirely by longer patch residency times when effort costs to leave were higher: F(2,26)=9.8, p=0.001; Mean difference (0% vs 30%) = 0.2s, t12=0.3, p=1; MD (30% vs 60%) = 2.5s, t12=4.4, p=0.002 (**Figure 5-5a & b)**. This behavioural change suggested an average effort cost of 6.5mL (compared to an average yield of 370mL per patch; **Figure 5-5d**).

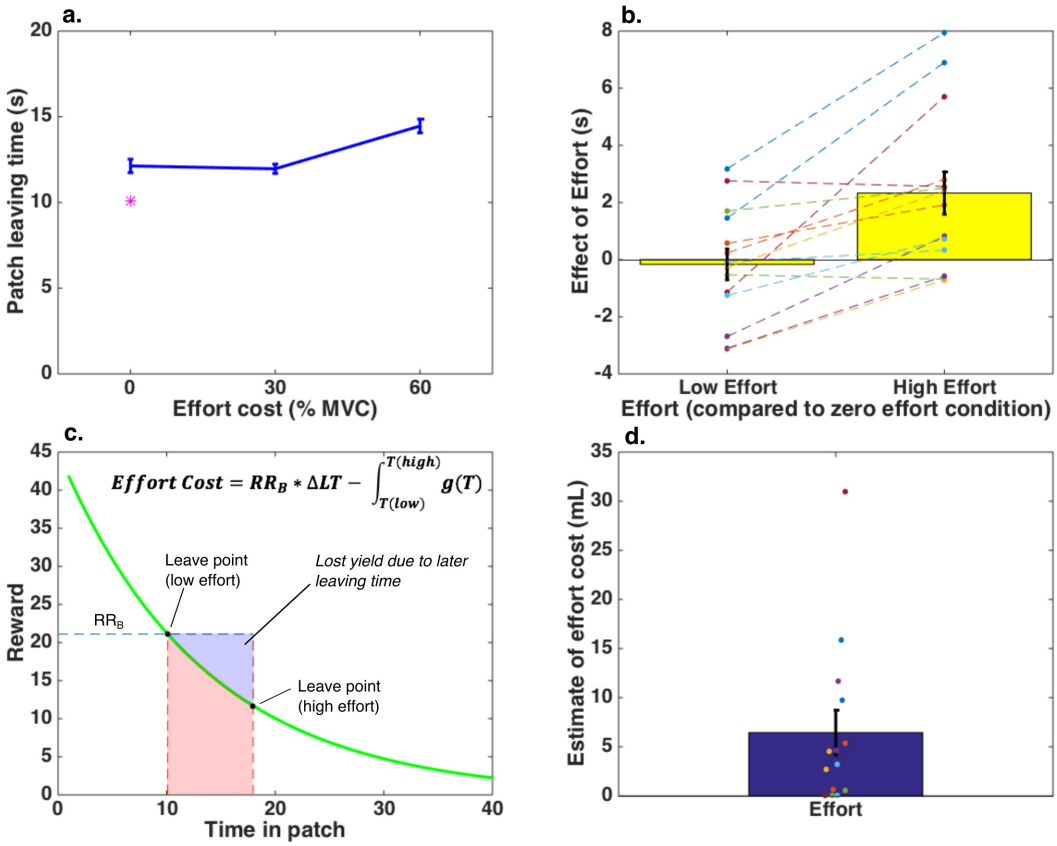


Figure 5-5. High effort costs increase patch residency time

(**a**) High, but not low effort costs were associated with increased patch residency times; pink asterisk = optimal leaving time when no effort costs present. (**b**) Individually de-meaned effects of low and high effort costs on patch leaving time; dotted lines represent change in time for each subject, and demonstrate that most subjects left patches later when effort costs were higher. (**c**) The change in patch leaving time (T(high eff) – T(low eff)) associated with higher effort costs can be used to estimate the cost of effort in the same units as reward, assuming that the leave time in the baseline (low effort) condition is the subject's estimate of the background reward rate, and therefore the opportunity cost of staying longer. (**d**) The cost of effort (blue shaded region) is simply this rate, multiplied by extra time spent in a high effort patch (blue + red shaded regions), minus the extra yield derived from the longer patch residency time (red shaded region). The increased time spent in each patch in the high effort condition was equivalent to the loss of 6.4 units of reward (on average) per patch.

5.5.3 Summary

High (but not low) effort costs shifted patch leaving behaviour towards longer patch residency times, consistent with MVT predictions.

5.6 Experiment THREE – reward and patch leaving behaviour

Aim: To determine the influence of foreground and background reward characteristics on patch leaving in healthy humans.

5.6.1 Methods

Participants: Twenty healthy volunteers (mean age 24 years, range 20-30) were recruited via a local database. 2 were subsequently excluded because: limited English meaning unable to understand instructions (1) and not attempting to engage with the task (1).

Experimental variables (Figure 5-6):

- **Delay Cost:** 6 seconds
- **Effort Costs (between patches):** nil
- **Patch-types:** Three patch-types, varied by the scale of the gain function: S = 32.5, 45 and 57.5; (decay rate the same in each)
- **Background environment:** Two types, varied by the proportion of high (S=57.5) and low (S=32.5) yield patch-types on each farm:
    - **Rich Environment:** 50% high, 30% medium, 20% low
    - **Poor Environment:** 20% high, 30% medium, 50% low
- **Blocks:** Two 10 minute blocks, with participants visiting each farm-type (rich or poor) once (order counterbalanced across subjects).

Statistical analysis

The primary analysis was conducted using a RM-ANOVA with leaving time the dependent variable, and patch type and environment predictor variables. For the patch

estimate I applied a Greenhouse-Geisser correction because of violation of the assumption of sphericity (ε=0.55, p<0.001).

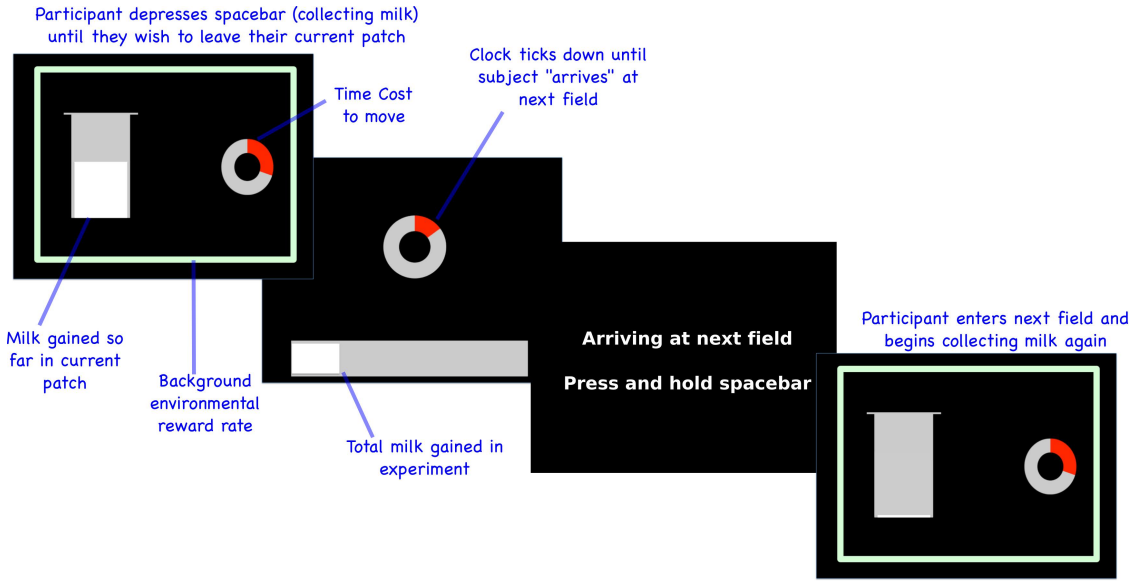


Figure 5-6. Reward paradigm

Participants made patch leaving decisions in two environments (denoted by the coloured border) – one with more high yield patches (rich environment) and one with more low yield patches (poor environment). Travel costs were fixed between patches.

5.6.2 Results

Both foreground (patch-type) and background (environment) reward rate had significant effects on patch leaving time. Participants left patches later when yield was higher: F(1.1,18.7)=137, p <0.001). On average, each increase in patch-type was associated with a six second longer residency time (t_{17}=13.7, p<0.0001). Participants also left patches later when background environment was *poorer:* F(1,17)=7.5, p=0.014. The average magnitude of the effect of background environment was 2.3s (t_{17}=2.73, p=0.014). There was no interaction between these two variables: F(2,34)=0.9, p=0.414 (**Figure 5-7a & b**).

Whilst the magnitude of foreground reward effect was significantly larger than predicted by MVT (MD=2.2s, t_{17}=5.0, p=0.0001), the effect of background

environmental was very close to the predictions of optimal foraging theory (MD=0.1s, t_{17}=0.1, p=0.92; **Figure 5-7b**).

In addition to these foreground and background reward effects, participants showed a significant bias to remain in (all) patch types for longer than predicted, on average leaving 7.9 seconds later than optimal foraging theory predicted (t_{17}=6.6, p<0.0001; **Figure 5-7a & c**). Overall however they collected on average more than 90% (mean 90.8%, std = 7%) of the available reward in the task (**Figure 5-7d**).

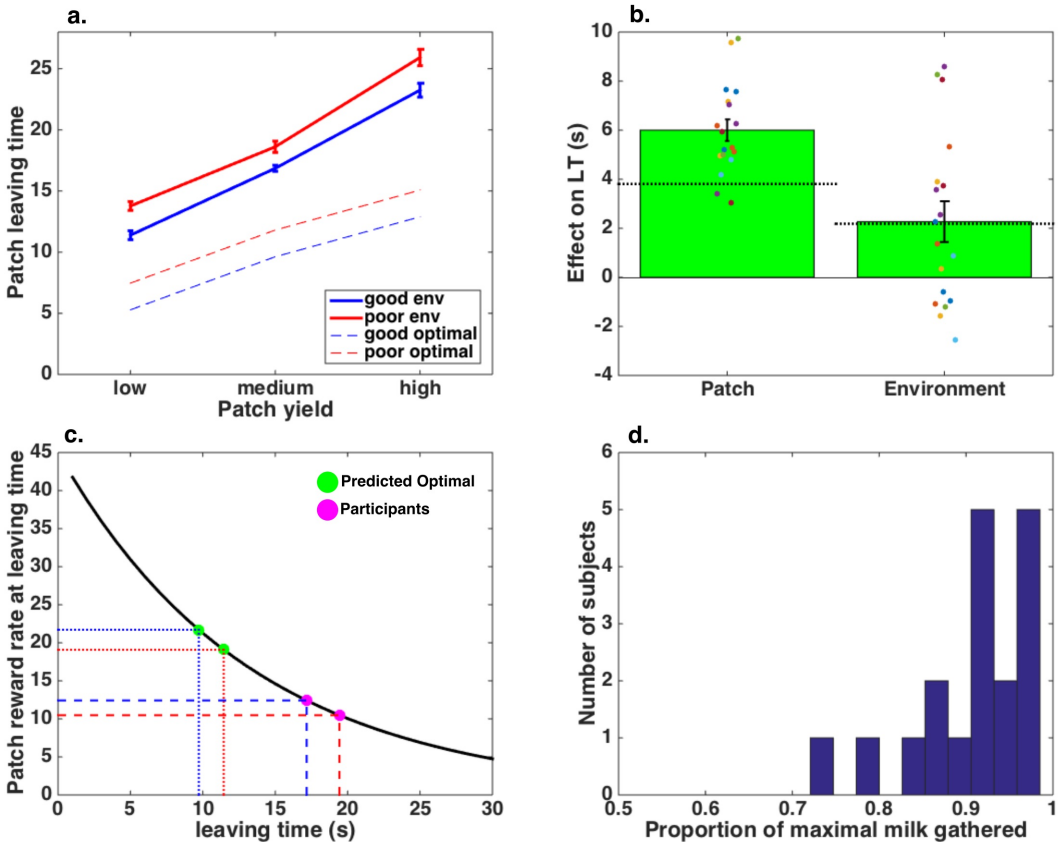


Figure 5-7. Effects of foreground and background reward on patch leaving

(**a**) Both foreground (patch-type) and background (environment) reward characteristics had a significant influence on patch leaving time, with participants remaining in patches longer when foreground reward rate was higher, and background reward rate was lower. (**b**) The magnitude of environmental effect was very close to optimal, whilst participants showed a greater than predicted effect of foreground reward rates (each subject is represented by one dot, and the predicted magnitude of each effect is shown by the dotted black line). (**c**) Participants showed a bias to stay in all patches longer than predicted (with optimal and actual (mean) patch reward rates at leaving

time shown for rich and poor environments). (**d**) Most participants had an overall optimality (proportion of possible reward collected) greater than 90%.

5.6.3 Summary

Human decision makers were sensitive to changes in foreground and background reward contingencies, consistent with MVT predictions. Although they showed a greater than expected sensitivity to changes in foreground reward rates, the average effect of changes in environmental context was very close to the predictions of foraging theory.

5.7 Experiment FOUR – human foraging behaviour in the face of continuously depleting patch resources

Aim: To determine if MVT variables independently affect human patch leaving behaviour in combination, and whether their effect is influenced by the presence of apathetic traits in healthy people.

5.7.1 Methods

Participants: Thirty eight healthy volunteers were recruited from local databases. 5 were excluded because: equipment failure (1), fell asleep during task (1); reported false beliefs about the tasks (2); unable to complete experiment (1). This left 33 subjects (17/16 female/male, mean age 25, range 18-37).

Experimental variables (Figure 5-8):

- **Delay Costs (between patches):** 8 and 12 seconds
- **Effort Costs (between patches):** 10% or 60% of MVC, held for 1 second
- **Patch-types:** Four patch-types in a 2x2 design, varied by scale and decay rate: S = 40 (low) or 60 (high); a = 0.075 (slow) or 0.1 (fast)
- **Background environment:** Two types, varied by the proportion of high and low yield patch-types on each farm:

    - **Rich Environment:** 80% high scale patches, 20% low
    - **Poor Environment:** 80% low scale patches, 20% high
- **Blocks:** Eight 7 minute blocks, with participants visiting each farm-type (combination of delay, effort and environment) once, order counterbalanced across subjects.
- **Skip trials:** To achieve a greater number of trials (and therefore patch leaving decisions) within the experimental time, as well as reduce the potential for physical fatigue, on 33% of leave trials, subjects did not have to exert physical effort, and instead waited only a mean of 4s. These "skip" trials were randomised throughout the study, and signalled to the participant only after they had made their decision to leave the patch (by a blue dot appearing centrally on the screen). This manipulation, which was present across all conditions, theoretically should not change the influence of the main experiment variables, but instead improves the average reward *rate across all conditions*, by reducing patch transit time. An alternate representation of its effect is that, for the short and long delay farms respectively, actual average delay costs were 6.67s and 9.33s, rather than 8 & 12 seconds.

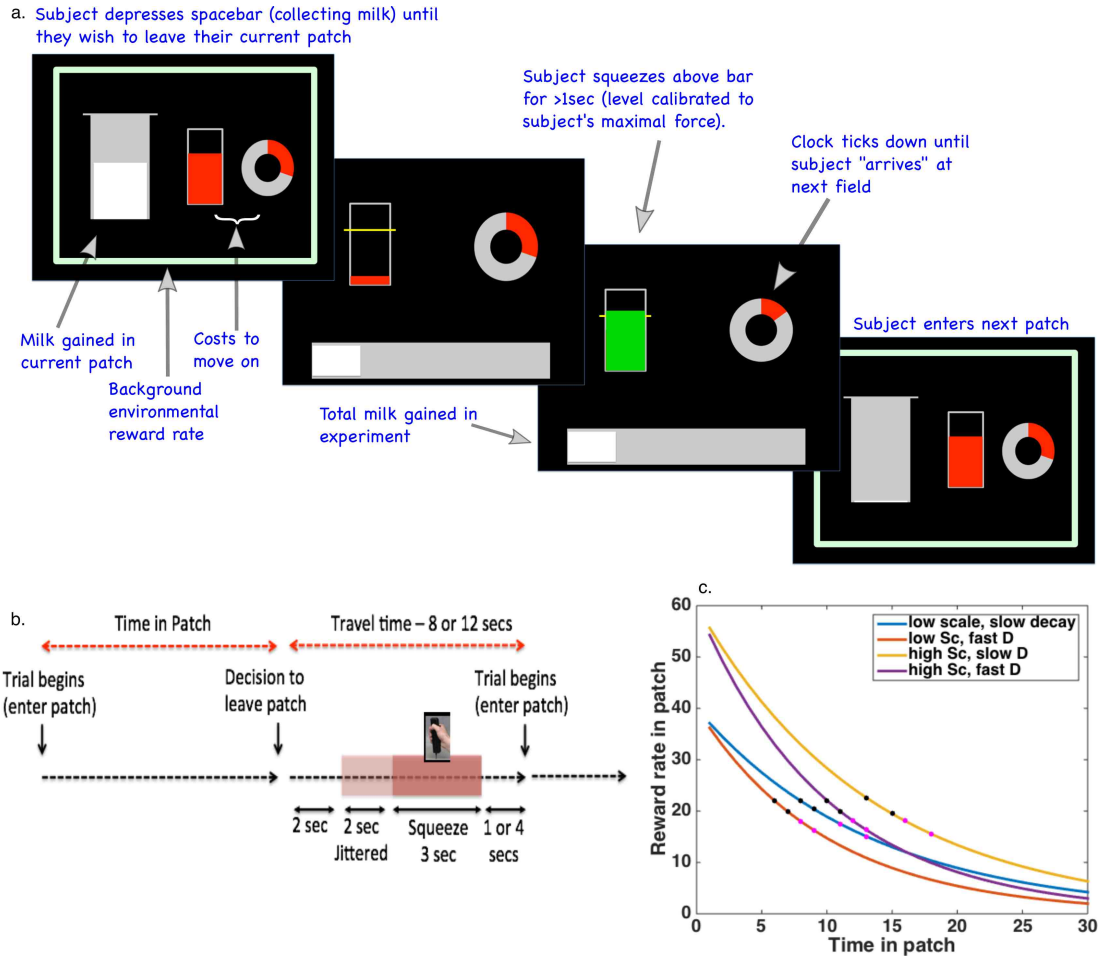


Figure 5-8. Combined experimental paradigm

(**a**) Participants decided how long to stay in their current field (patch), in which reward rate decreased in an exponential manner, before choosing to move onto the next field. Moving on meant incurring a time cost, during which no milk could be collected, as they "walked" to the next field, and, and required an effort cost (1 second squeeze on a handheld dynamometer to "climb a fence"). When they entered a new field the reward rate would reset to the maximum (for that particular field type) and again exponentially drop off. Subjects were aware they had only a *limited amount of time on a farm*, but that there were an *unlimited number of patches available*. (**b**) Timings for a single trial. (**c**) Optimal leaving times (not accounting for effort costs). Superimposed on the 4 different patch reward curves are the optimal leaving times (for short and long delays) in the rich environment (black dots) and poor environment (magenta dots), demonstrating a wide range of predicted leaving times.

Statistical analysis

Two complementary methods were used to analyse this experiment. I used a general linear model (*glmfit* in Matlab) to assess the main effects of delay, effort, environment and patch reward characteristics (scale and decay) on patch leaving time in each subject. I also used a hierarchical linear mixed effects model specifically to check for

higher-level interactions within the experiment. This was run using the *fitlme* function within MATLAB, Mathworks. Delay, effort, background environment, patch type and their interactions were entered as fixed effects. Subject and the higher level interactions between subject and other variables were entered as random effects (intercept only), consistent with current recommendations (Barr et al., 2013). The model which minimised the BIC was used for the final analysis, but it should be noted that the significance of the effects presented here did not vary based on which random effects were included.

5.7.2 Results

Influence of MVT parameters on patch leaving in humans

At a group level, there were significant effects of all variables on patch residency time. Longer transit times, higher effort costs, poorer background environment, slower decay rate of the reward function and higher reward function scale were all associated with later patch leaving: *Delay* PE=0.46, t_{33}=2.77, p=0.0092; *Effort* PE=0.59, t_{33}=3.52, p=0.0013; *Environment* PE=0.51, t_{33}=4.07, p=0.0003; *patch decay*=2.39, t_{33}=13.5, p < 0.0001; *patch scale*=1.58, t_{33}=13.4, p<0.0001 **Figure 5-9**. These effects translated to a change in patch leaving time of 1.0s, 1.2s, 1.1s, 3.3s and 4.8 seconds respectively, when collapsing across all other variables.

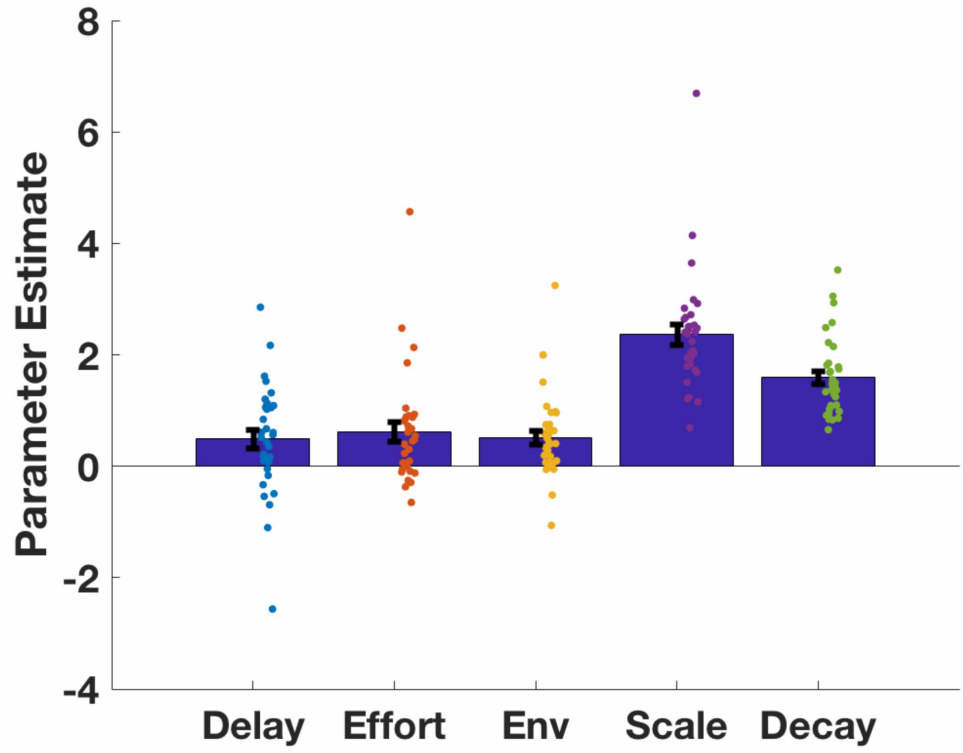
Analysis using a generalised linear mixed effects model produced analogous results, with significant main effects of all variables, and no interactions; *Delay*: F(1,34)=9.1, p=0.0047; *Effort*: F(1,34)=12.3, p=0.0013; *Environment*: F(1,80)=14.0, p=0.0004; *Patch*: F(1,102)=24.3, p<0.0001 (**Figure 5-9**).

Association between apathy traits and sensitivity to MVT parameters

Higher levels of apathy traits were associated with significantly greater sensitivity to background reward environment (ρ_{34}=0.42, p=0.012), but not foreground (patch) properties (Scale: ρ_{34}=0.05, p=0.80; Decay: ρ_{34}=0.03, p=0.86). There was no significant relationship between apathy traits and the effect of effort costs (ρ_{34}=0.16, p=0.36) or delay costs (ρ_{34}=0.22, p=0.20). Furthermore, average patch leaving time across the entire experiment was not significantly correlated with apathetic traits

(ρ_{34}=0.22, p=0.21). To investigate the driving factors of the association between apathy traits and background environment further, I divided the sample into high and low apathy trait levels using a median split. I performed a RM-ANOVA, using leaving time as the dependent variable, environment as a within subject variable, and apathy status as a between subject variable, to test the hypothesis that the effects of apathy would occur mainly in the poor environment (with apathetic subjects staying longer in patches in this condition). However although there was an expected main effect of environment on leaving time ($F(1,32) = 16.6$, $p < 0.001$), there was no interaction between environment and apathy ($F(1,32) = 1.2$, $p=0.29$). That is, the effects of apathy on leaving time were present in both rich and poor environments. Consistent with the Spearman correlation reported above, although subject's with higher levels of apathy trended towards leaving patches later (mean difference 1.7s), this difference was not statistically significant ($F(1,32) = 2.1$, $p=0.16$; **Figure 5-10**).

Higher self-report of depressive symptoms (GDS-depression subscale) was not significantly associated with any of these task variables, and nor did this metric correlate with apathy traits (ρ_{34}=0.04, p=0.83).



ANOVA marginal tests: DFMethod = 'Satterthwaite'

Term	FStat	DF1	DF2	pValue
'(Intercept)'	709.42	1	34.067	2.1646e-24
'delay'	9.1229	1	34.423	0.0047345
'effort'	12.356	1	34.054	0.0012652
'env'	13.969	1	79.658	0.00034818
'patch'	24.323	1	102.28	3.1611e-06
'delay:effort'	0.072777	1	35.064	0.78892
'delay:env'	2.2279	1	50.783	0.14173
'effort:env'	0.99963	1	46.934	0.32253
'delay:patch'	0.85668	1	718.65	0.35498
'effort:patch'	2.8919	1	698.58	0.089473
'env:patch'	0.26924	1	742.4	0.604
'delay:effort:env'	0.12344	1	694.18	0.72544
'delay:effort:patch'	0.519	1	711.03	0.4715
'delay:env:patch'	0.27393	1	713.14	0.60087
'effort:env:patch'	0.22756	1	701.15	0.63348
'delay:effort:env:patch'	0.084397	1	720.67	0.77151

Figure 5-9. Main effects in combined patch leaving experiment

Longer delays, higher effort costs, poorer background environment, and better foreground environments (patch scale and decay) were all associated with later patch leaving times (**top**). A hierarchical linear mixed effects model confirmed the main effects of all these variables, and did not show any significant interactions (**bottom**).

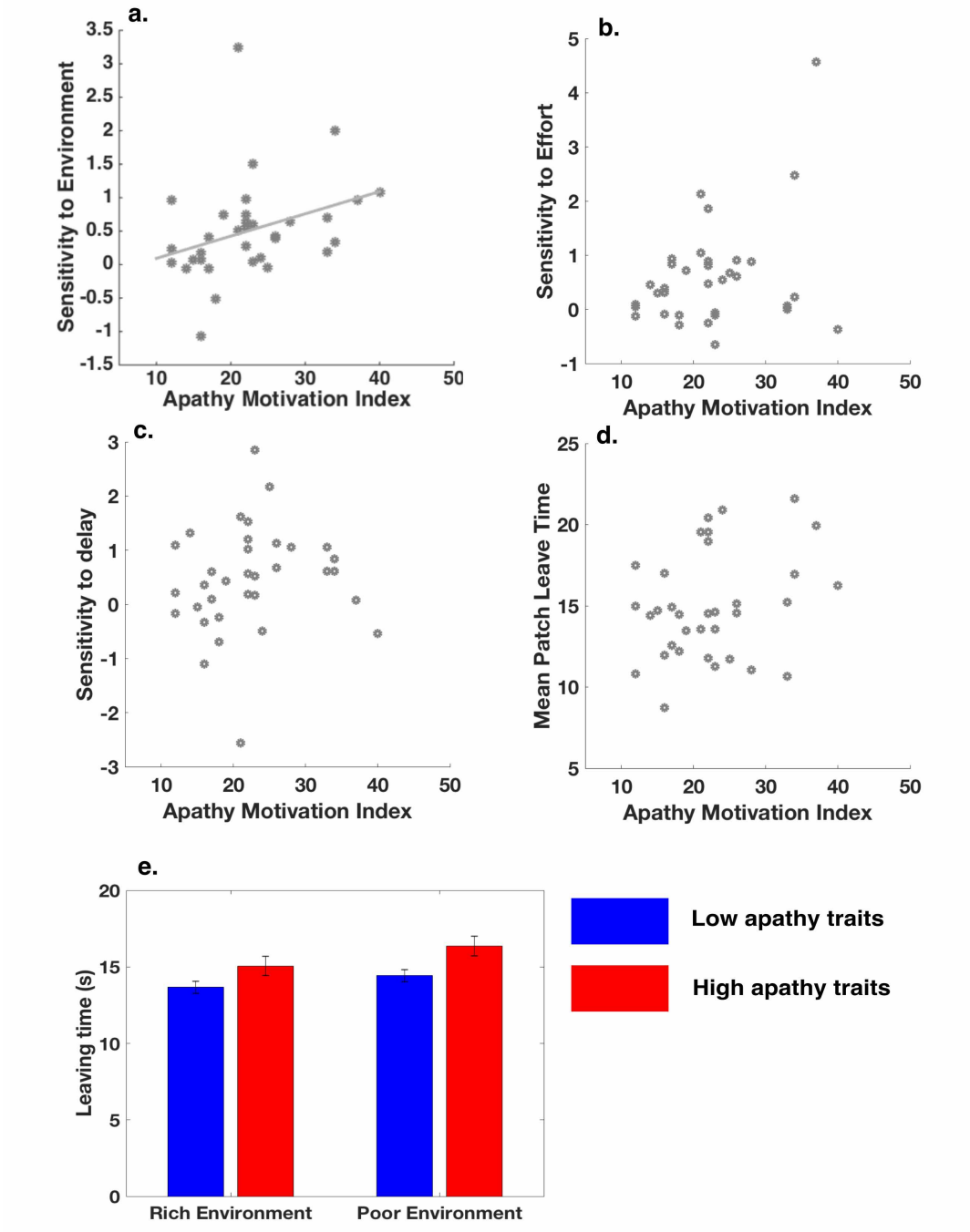


Figure 5-10. Relationship between apathy traits and patch leaving

Higher apathy traits (measured by the apathy motivation index) were associated with an increased sensitivity to background reward environment (p=0.01), but not effort or delay costs (p=0.36 and p=0.20 respectively – **a, b & c**). There was no significant correlation between mean patch leaving time (across the experiment) and level of apathy traits (**d**). Subjects with higher apathy traits showed a non-significant trend to leave patches later, in *both* rich and poor environments (**e**).

5.7.3 Summary

This final experiment demonstrates independent effects of the different components of MVT on patch leaving behaviour in a more complex behavioural task than experiments 1-3. Higher apathy scores were positively associated with sensitivity to one component of reward – the background reward environment. There was also a small trend towards more apathetic participants leaving patches later, but this was not statistically significant.

5.8 Control analysis – effects of time on task

For experiments 1,2 and 3 I checked for any systematic shifts in leaving time behaviour related to time elapsed in the experiment, as a basic check for significant learning, fatigue or other confounding factors (**Figure 5-11**).

For experiment one, in which each condition block (delay cost) was sampled twice, I compared the mean in the first block to the mean in the second, using a RM-ANOVA (Delay and Block within subject variables). There was no main effect of Block: $F(1,17)=0.9$, $p=0.36$, nor an interaction between block and delay: $F(2,34)=0.4$, $p=0.67$. As previously demonstrated there was a strong main effect of delay: $F(2,34)=41.4$, $p<0.001$ (**Figure 5-11a**).

In experiment two, each effort condition was sampled twice, allowing for the same comparison as in experiment one. There was no main effect of Block: $F(1,13)=0.5$, $p=0.48$, nor an interaction between Block and Effort: $F(2,26)=0.7$, $p=0.51$. As previously demonstrated there was a main effect of Effort: ($F(2,26)=9.3$, $p=0.001$, **Figure 5-11b**). Additionally, to check if patch residency time may have changed *within* a block (e.g. lengthening because of fatigue effects), I compared the mean leaving time in the first and final three trials of each block (for each subject). This demonstrated no main effect of Timing (*start vs end* of block): $F(1,13)=2.7$, $p=0.12$, and no interaction between effort level and timing: $F(2,26)=0.7$, $p=0.51$, **Figure 5-11c**.

In experiment three, patch types were interleaved within each block (poor and rich environment). For each subject I compared the mean leaving time in the first 3 trials of

each condition (combination of patch-type and environment) with the mean leaving time in the final 3 trials of that condition using RM-ANOVA (both condition and timing (start or end) were within subject variables). There was no main effect of timing: $F(1,13)=0.05$, $p=0.84$, nor a condition by timing interaction: $F(5,65)=0.24$, $p=0.94$. As expected there was a strong effect of condition: $F(2.4, 31.8)=60.4$, $p<0.001$, (**Figure 5-11d**).

In sum, these analyses do not demonstrate any potential evidence of either learning or fatigue influencing patch leaving decision making in these experiments.

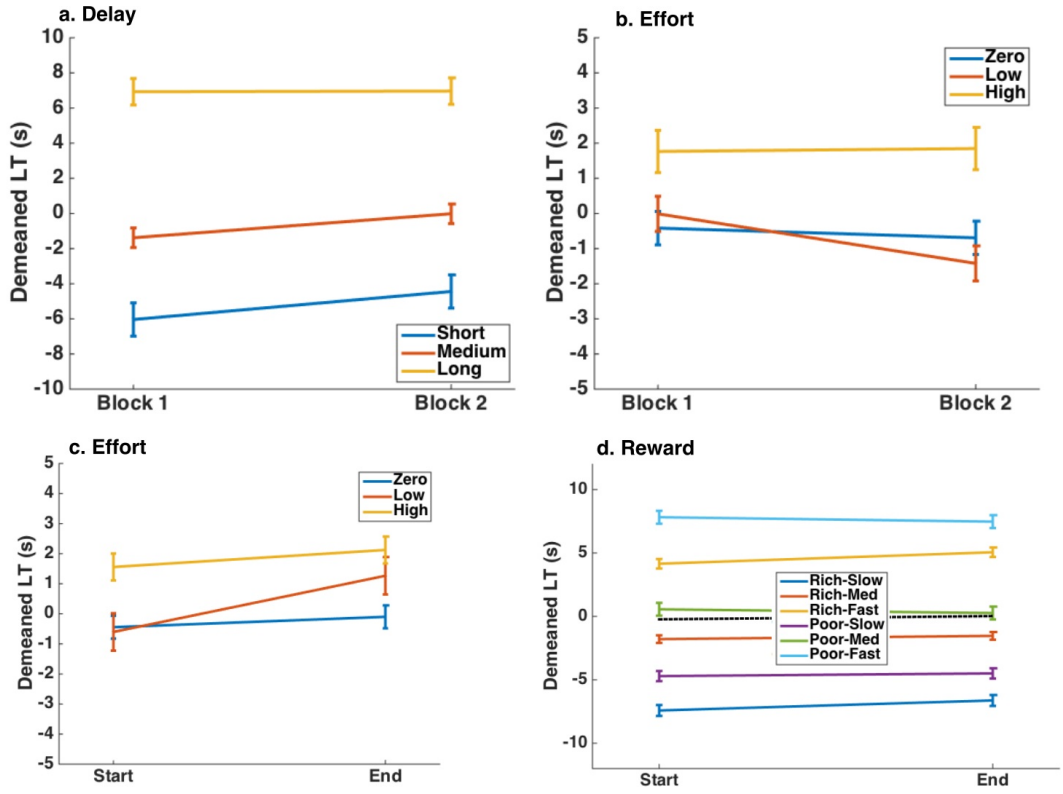


Figure 5-11. Patch leaving times were not altered by stage of task

Patch residency time did not significantly change, for a given condition, between first and second block (delay and effort tasks – **a & b**). There was no main effect of timing (start vs end of experiment) on patch residency time in the effort experiment (**c**). There was also no main effect of timing (start vs end) on patch residency time in experiment three (in which foreground and background reward rates varied) – each condition is plotted with a different colour, and the mean effect across conditions is shown by the dotted black line, (**d**).

5.9 Discussion

The experiments presented here represent, to the best of my knowledge, the first systematic investigation of patch leaving behaviour in humans. The results of these experiments provide strong evidence that humans are sensitive to the different components specified by the marginal value theorem when making patch-leaving decisions. Moreover, the effect that *changes in these variables* has on patch residency time is broadly (and in some cases very closely) aligned with the predictions of optimal foraging theory, suggesting that this theoretical account – which emphasises a comparison between foreground and background reward rates – is a valid construct to apply to the behaviour of human decision makers. These effects were present when tested in isolation (experiments one to three), but crucially were also found in a more complex setting (experiment four). Furthermore, the presence of apathy traits correlated with the extent that changes in reward contingencies – specifically background environmental reward rates – altered patch leaving behaviour, whereas the same relationship was not present for either effort or delay costs.

Perhaps unsurprisingly, longer transit time between patches was strongly associated with increased patch residency time, when tested in isolation (experiment one) and in a more complex paradigm (experiment four). This is one of the most often studied components in animal patch leaving behaviour, and these results accord with earlier results in the behavioural ecology field ((Nonacs, 2001)), as well as general observations in human work (Constantino and Daw, 2015; Hutchinson et al., 2008). However, the design of these experiments allowed for an accurate estimation of the *magnitude* of the effect of changing delay costs (increased time spent in patch). Intriguingly, participants adjusted their patch leaving times in a manner very close to optimal foraging theory predictions in both experiments, although they did show an increased sensitivity to the longest delay costs in experiment one.

High effort costs also biased subjects to stay in patches longer, although interestingly there was no change in behaviour between zero and low effort costs (experiment two). This accords with recent work showing that physical effort is not represented linearly, but often follows a parabolic function (Chong et al., 2017; Hartmann et al., 2013;

Klein-Flugge et al., 2016). For this reason, as well as to limit potentially confounding features (related to the squeeze itself), experiment four included just low and high effort levels. Very little work has investigated the effects of effort costs on foraging decisions. Although its impact is acknowledged, and clearly represented within optimal foraging theory, the calculation of effort costs in naturalistic settings is problematic, and often ignored (Hayden et al., 2011), but see (Cowie, 1977). Here, I deduced (in units of reward) the effect of high versus low effort, based on the opportunity cost of participant's increased patch leaving times. Although the magnitude of reward foregone was small compared to the total reward harvested from each patch, it must be remembered the manipulation was also small (a one second squeeze compared to ~ 15 seconds of reward collection), and the change in behaviour was consistently observed across nearly all subjects. This method is, however, somewhat circular, as it is based on estimates derived from the participants own behaviour. An alternative approach would be to measure effort expenditure in a metabolically meaningful way using physiological techniques (Shadmehr et al., 2016). Future research could investigate if these more biologically relevant measures of effort provide better predictions of foraging behaviour.

Whilst delay and effort varied the background reward rate by altering the costs of moving on from a patch, changes in the distribution of patches varied it by altering the environmental reward properties. Optimal foraging theory predicts that participants should adjust behaviour to leave all patches *earlier* when the background environment is richer (more rewarding). Remarkably, subjects in experiment three adjusted their behaviour to, on average, within 0.1s of the *optimal change*, despite their bias to stay later. As with the effect of delay costs, it is the closeness of the *magnitude of effect* to MVT predictions, rather than its raw presence, that provides the strongest support for the foraging construct as a useful way to view this behaviour.

Changes in foreground (patch) reward rates exerted a strong influence on patch leaving decisions in experiments three and four. The paradigm settings were such that the magnitude of change in patch residency time between the patch types should have been greater than for the other variables manipulated. Furthermore, the paradigm required participants to specifically attend to the patch properties on every trial, creating a mismatch in saliency between the variables that determined foreground and

background reward rates. While this may not seem ideal, this situation is probably closer to a 'real world' decision making setting, when your current (foreground) activity will also be more salient than the other alternatives. Additionally, the fact that foreground information did not "wash out" the effects of other variables suggests that this concern is of minimal significance in interpreting the results of the study.

The demonstrated behavioural sensitivity to MVT predictions in healthy humans opens the possibility of using this foreground/background construct of effort-based decision making to understand neurobehavioural deficits such as apathy. In this healthy young population, the degree of self-reported apathy traits was associated with a specific feature of the task – the background environmental reward context. Individuals with higher apathy levels adjusted their behaviour to a greater degree when background environment shifted from rich (high proportion of high yield patches) to poor. In interpreting this result in the broader apathy context it is important to observe that it is not yet clear how the presence of apathetic traits in otherwise healthy individuals maps onto the clinical syndrome of apathy that develops in a patient with a neurological disorder. Nevertheless it is striking that apathy in this experiment is specifically associated with sensitivity to background reward rate – to some degree mirroring the association between reward level and apathy demonstrated in chapters 2-4. Interestingly apathy level did not correlate with raw patch leaving time, although there was a non-significant trend towards people with more apathy traits remaining in patches for longer. Based on the reward * apathy interaction demonstrated in earlier chapters, in which apathetic patients are not incentivised to act when reward outcomes are low, I hypothesised that apathetic participants would leave patches in poor environments relatively later (compared to the non-apathetic participants) than patches in rich environments. However this interaction was not significant with more apathetic individuals tending to leave patches later in both environment types (albeit with a greater change in leaving time than their non-apathetic counterparts). Further work is required to understand this association better, an issue focussed on in **Chapter 6**.

Participants in all experiments demonstrated a background bias to leave fields later than predicted, *across all conditions*. This tendency to "overharvest" is commonly observed in animal foraging experiments (Constantino and Daw, 2015; Hayden et al., 2011; Nonacs, 2001; Stephens et al., 2007; Wikenheiser et al., 2013). Different

explanations are possible. The marginal value theorem, on which our optimal predictions are based, is a simple model and does not account for all factors that may influence patch-leaving decisions. These un-modelled factors include risk of predation when moving between patches, the possibility of organisms wishing to avoid a lower bound of energy stores (which could for example lead to starvation in certain contexts such as when patches are sparsely distributed), other activities (e.g. grooming, finding a mate), and also potential neuro-computational limits (Bateson and Kacelnik, 1996; Nonacs, 2001; Stephens, 2008). Any of these factors could potentially contribute to the observed bias from the optimal leaving time predicted by the simple MVT model.

Another potential explanation of the tendency to overharvest is the *status quo bias.* This describes the inherent resistance observed in human behaviour to change – i.e. the propensity to maintain a previous decision/strategy (Samuelson and Zeckhauser, 1988). This bias is more noticeable when decisions are difficult, and overcoming it has been associated with interactions between pre-frontal cortex (inferior frontal gyrus) and subthalamic nucleus (Fleming et al., 2010). These possibilities are also not mutually exclusive. For example it may be that status quo bias can, when viewed through a foraging lens, be understood as a reasonable strategy in situations where the background environment reward rate is difficult to predict, in a similar way that the phenomenon of temporal discounting (the subjective devaluing of rewards when there is a delay to receiving them) can be explained as an appropriate foraging strategy in many situations (Stephens, 2008). A final point is that although uncertainty about the foraging environment could also lead to a more conservative patch leaving strategy, the experiments were designed to minimise this factor (externally cuing variables and training subjects prior to the experiment) and no systematic changes in behaviour were present across or within blocks, as would have been expected if significant learning about an uncertain environment was occurring. Therefore this factor is unlikely to explain the observed bias.

Despite this bias to overharvest (which meant subjects completed fewer trials than initially predicted during experimental design), participants performed close to optimally across all experiments. They were sensitive to all manipulated variables in line with MVT predictions, and collected more than 90% of the available reward in the majority of cases. These results suggest that foraging theory provides a valid construct

within which to understand the behaviour of human decision makers. It is worth mentioning that, while foraging theory assumes net energy gain as the underlying metric which organisms maximise, this does not necessitate a direct neural representation of energy. Rather, it seems more plausible that decision making systems would have evolved to behave *as if* they were maximising this metric (with its obvious fitness advantages) without needing an actual representation, in much the same way that neural systems can express homeostatic-like behaviour without requiring a 'target' set-point (Berridge, 2004). In contrast, and in keeping with current concepts within decision making neuroscience, it would seem very likely that the separate components tracked to make patch-leaving decisions, as well as an integration of these components, would have a direct neural representation (Hayden et al., (Kolling et al., 2016); Kolling et al., 2012; Pearson et al., 2014). Future work will investigate whether such a patch-leaving signal indeed accumulates to drive behaviour, in a manner akin to the ramping neural models used to describe perceptual decision making (Gold and Shadlen, 2001), and whether differences in this physiological process relate to apathy.

Although this work provides the first (to my knowledge) thorough account of classic patch leaving behaviour in human decision makers, previous work has examined aspects of these questions. Using a task in which rewards occurred only intermittently within patches (rather than following a continuous distribution as in the current experiment) and a stochastic patch-type environment, Hutchinson et al found that simple heuristics better accounted for patch leaving behaviour than an MVT based model (Hutchinson et al., 2008). However as discussed earlier this may have been related to the behavioural paradigm used, in which participants would have struggled to accurately predict salient reward information and may therefore have reverted to simpler strategies such as leaving after receiving 5 rewards (or equivalent). In contrast, using a task in which reward encounters were also discreet, but less variable, Constantino and Daw demonstrated that participants changed their behaviour to optimise reward harvest in a manner that was better explained by an MVT-based theory of learning rather than a more classical temporal difference learning model (Constantino and Daw, 2015). A recent fMRI study investigated the mechanisms of voluntary persistence towards rewards, using a decision making paradigm with a foreground/background structure in which participants had to choose when to move on from the current trial, in which a reward delivery was stochastic. Cues signalled the

context – essentially the likelihood that reward would be delivered after a short versus longer delay, and the authors found vmPFC activity tracked the subjective value of persisting with the current trial. This demonstrated that the valuation system strongly implicated in economic binary choice models is also important for guiding choices over extended temporal periods (McGuire and Kable, 2015). However the behavioural paradigm, whilst superficially evoking a remain versus leave decision, was too simplistic to adequately test hypotheses regarding the mechanisms underlying patch leaving behaviour in humans, an important focus for future work in this area.

It is important to consider potential criticisms of this novel design. Although there is a mismatch in saliency between foreground and background variables, as discussed earlier this is unlikely to be a significant issue. Another potential criticism is that reward rate is correlated with time in patch, meaning it is harder to exclude the possibility of participants simply choosing a 'time' based policy for switching. However, participants were sensitive to the different MVT variables, rendering this point of negligible significance. Furthermore, the magnitude of effect of these variables was, for the most part, in line with MVT predictions, again arguing against simple heuristics as an explanation for behaviour. The task itself does take ~8-10 minutes to explain. For this reason a standardised description with visual aids was utilised, and participant understanding checked before commencing the experiment. Learning effects were minimised by the use of external cues and a thorough task explanation and practice session, and furthermore analysis found no evidence of their presence.

In conclusion, this chapter demonstrates that healthy human decision makers are sensitive to the components of optimal foraging theory to a degree which is very close to model predictions. This emphasizes the utility of the foreground/background approach, which may provide a framework within which to understand the computations underlying effort based decision making, and, as I explore in the following chapter, to understand neurobehavioural disorders such as apathy.

6 Chapter Six – Reward context, apathy and dopamine

6.1 Chapter Summary

Despite emerging evidence that foreground/background models of decision making provide a powerful tool to explain naturalistic behaviour, little is known about the influence of factors such as the dopaminergic system on this class of decisions, although it is undoubtedly crucial to other aspects of cost-benefit decision making. Still less is known about whether disruption of these putative mechanisms could underlie the reduction in goal directed behaviour that characterises neurobehavioural syndromes such as apathy.

In this chapter I investigate the effects of changing dopamine levels and the presence of apathy on the ability to use foreground and background reward information to guide patch leaving decisions. Across two experiments – in healthy older people and patients with Parkinson's disease – utilising the reward patch-leaving paradigm developed in the previous chapter, I found that changes in tonic dopamine levels altered the influence of background, but not foreground, reward rate on patch leaving behaviour. Furthermore, in Parkinson's disease the presence of apathy modulated this dopaminergic effect on background reward context. That is, as with healthy participants, changes in dopamine levels altered the effects of environment on patch leaving, but only in patients who were apathetic. These results associate tonic dopamine levels with utilisation of information about background reward environment, whilst revealing a mechanism by which disruption of dopaminergic pathways could lead to apathy.

6.2 Introduction

The mesolimbic dopaminergic system plays a crucial role in motivating behaviour towards goals (Hamid et al., 2016; Kurniawan et al., 2011; Le Bouc et al., 2016; Salamone and Correa, 2012). These dopaminergic signals develop across multiple time scales, and whilst a large body of evidence implicates phasic (fast changing) dopamine

signals in encoding prediction error (Hauser et al., 2017; Schultz, 2007) or salience (Berridge, 2012; Redgrave and Gurney, 2006) to drive behaviour and learning, less is known about tonic (slower changing) signals. A prominent theoretical model of tonic dopamine suggests that it encodes information about background reward rate, and therefore the opportunity cost associated with a chosen behaviour (Niv et al., 2007). This model predicts that organisms should increase their response vigour in more rewarding environments (to reduce the opportunity cost of their actions) and is supported by some empirical evidence in animal and human studies (Beierholm et al., 2013; Guitart-Masip et al., 2014; Hamid et al., 2016; Holroyd and Coles, 2008; Niv et al., 2007; Salamone and Correa, 2012). However recent work has questioned this account of tonic dopamine (Zenon et al., 2016), and formal evidence linking dopamine to background reward rate is lacking.

An accurate representation of environmental background reward rate is a crucial component of foraging models of behaviour (Stephens and Krebs, 1986). These models provide a powerful tool to explain naturalistic animal behaviour, and emphasise decisions in which foreground – *what you are doing right now* – and background – *what else you could be doing* – reward rates are directly compared (Pearson et al., 2014; Stephens, 2008; Stephens and Krebs, 1986). A fundamental foraging decision, termed the patch leaving problem, describes the situation where an animal must decide how long to remain at a location (patch) with depleting resources before moving on to another patch in their environment as they seek to maximise their overall energy gain (Stephens and Krebs, 1986). The optimal solution to this problem, described by the marginal value theorem (**Figure 1-5**), is to leave when the instantaneous foreground reward rate drops below the average background rate (Charnov, 1976). Neural evidence for this comparison process driving foraging behaviour has been described in macaques (Hayden et al., 2011) and humans (Kolling et al., 2012), but it remains unclear how information about background reward context is encoded.

The background reward rate conceptualised within foraging frameworks shares identical properties to the background rate that opportunity cost models link to tonic dopamine signals (Niv et al., 2007; Pearson et al., 2014; Stephens and Krebs, 1986). Indeed, background reward rate in optimal foraging theory signals the opportunity cost

of the current action-set – what is missed out on by persisting with the current (foreground) behaviour. Consequently, foraging theory makes clear predictions about the effect of changing background reward rates on switching behaviour, predictions that have been confirmed behaviourally in animals and humans (Hayden et al., 2011; Nonacs, 2001 & **Chapter 5**). Foraging models therefore provide an important and biologically relevant framework in which to test predictions about dopamine and background reward rate, however very little is known about the influence of the dopaminergic system on this class of decisions (but see (Constantino et al., 2017).

The intersection of dopamine and patch leaving behaviour may be particularly relevant when considering the mechanisms that underlie neurobehavioural disorders such as apathy. Particularly in Parkinson's disease, apathy has been associated with abnormalities within the mesolimbic dopaminergic system (Remy et al., 2005; Santangelo et al., 2015; Thobois et al., 2010). However recent work demonstrated that apathy and changes in dopamine levels had dissociable effects on an individual's willingness to exert effort for reward (Le Heron et al., 2018 & **Chapter 4**). Importantly though, this study did not manipulate background reward rates, with patients simply required to consider the reward outcome of the current potential action. It therefore remains an important, unanswered question as to whether changes in the mesolimbic dopaminergic system could drive apathetic behaviour by affecting the representation of background reward rates.

How might this lead to the reduced goal directed behaviour that characterises apathy? Apathetic patients frequently report "It doesn't seem worth it", or "I can't be bothered" when trying to explain their lack of engagement with potential activities. A general hypothesis, within the framework of optimal foraging theories, is to view apathy as a failure of patch leaving. That is, apathetic patients fail to switch from their current (foreground) activity (which may be for example sitting on the couch) because either their representation of the background reward rate is pathologically low, or they fail to integrate background and foreground reward information to drive behaviour change. Support for this hypothesis comes not only from the association between changes in the dopaminergic system and apathy, but also from an anatomical overlap between brain regions considered crucial for driving foreground/background decision making (particularly anterior cingulate cortex) and areas that are consistently implicated in the

development of apathy (Hayden et al., 2011; Kolling et al., 2016; Le Heron et al., 2017).

Here, I investigated the role of dopamine in decision making that requires a comparison between foreground and background reward rates, and whether these effects were influenced by pathological loss of motivation. Specifically, I tested the hypotheses that, firstly, changes in tonic dopamine levels would alter the influence of background reward environment on patch leaving behaviour, and secondly, that this dopaminergic influence on background reward rate would be modulated by the presence of apathy.

To address these issues I performed two experiments using a computer-based behavioural paradigm in which foreground and background reward rates were independently manipulated. In the first experiment, over two sessions healthy elderly participants made patch-leaving decisions following administration of either cabergoline – a selective D2-receptor agonist – or placebo. In the second experiment, apathetic and non-apathetic patients with Parkinson's disease completed the same task, ON and OFF their normal dopaminergic medications. Thus, I was able to examine the independent effects of apathy and dopamine on foreground/background decision making, and specifically look for interactions between these two variables and the different reward components manipulated in the task.

6.3 Methods

6.3.1 Ethics

This study was approved by the local ethics committee and written consent was obtained from all subjects in accordance with the Declaration of Helsinki.

6.3.2 Recruitment and protocol

Experiment ONE: Thirty healthy, elderly (age range 60 - 78) participants were recruited from the local Oxfordshire region. Potential participants were screened for

the presence of neurological, psychiatric or cardiovascular diseases, or for the use of medications that could interact with Cabergoline, and excluded if any of these were present. The protocol was a randomised, placebo-controlled double-blind study, with participants tested in two separate sessions, once following administration of a single dose of 1mg Cabergoline, and once following administration of an indistinguishable placebo tablet. The order of testing was counterbalanced across drug manipulation, gender and order of background foraging environment (rich-poor or poor-rich). One subject was subsequently excluded because a core metric of task performance (variance in leaving times per condition) fell outside three standard deviations of the mean variance, leaving 29 participants for analysis.

Experiment TWO: Thirty six patients with a clinical diagnosis of idiopathic Parkinson's disease (PD), confirmed by myself and one other neurologist prior to study recruitment, were recruited from local movement disorders clinics in the Oxfordshire area. Inclusion criteria included an absence of PD dementia or other major neurological or psychiatric conditions. Patients with clinical apathy were intentionally recruited, such that the final study population had a roughly even split of apathetic and non-apathetic patients. These patients were tested in two separate sessions – once ON their normal dopaminergic medications, and once following an overnight withdrawal of these drugs (OFF). The order of testing was counterbalanced across apathy status and order of background foraging environment. One patient was subsequently excluded due to failure to understand the task and decisions that fell outside of 3 SD from the group mean, leaving 35 patients.

A separate cohort was also recruited from the local Oxfordshire region as a control group (gender and age matched) for the PD patients. This group was free from cognitive impairment or apathy. Two were subsequently excluded because of concerns about their behaviour (not engaging with the task), leaving a total of 29 participants.

Demographics for all participants are presented in **Table 6-1**. Of note, the majority of these subjects also undertook the study reported in **Chapter 4**, so the association between quality of life and apathy is not re-reported here.

Measure	Cabergoline study participants	Healthy elderly controls	Parkinson's disease	Control vs Parkinson's disease (p value)	Parkinson's disease – no apathy (LARS ≤ -22)	Parkinson's disease – apathy (LARS >-22)	No apathy vs apathy (p value)
Number	29	29	35	n/a	17	18	n/a
Age	68.2 (±4.5)	68.6 (±8.2)	67.7 (±8.0)	p=0.66	68.4 (±6.7)	67.2 (±9.2)	p=0.67
Gender (F/M)	11/18	10/18	11/24	p=0.79^	7/10	4/14	p=0.29^
Apathy (LARS)	-21.4 (±4.5)	-26.7 (±4.1)	-21.1 (±6.5)	**P=0.0002**	-26.7 (± 3.7)	-15.9 (±3.3)	**p<0.0001**
Hoehn & Yahr stage	n/a	n/a	2.2 (±0.5)	n/a	2.2 (±0.5)	2.1 (±0.5)	p=0.83
UPDRS - total	n/a	n/a	83.6 (25.4)	n/a	75.2 (±25.9)	91 (±23.2)	p=0.08
UPDRS motor score ON	n/a	n/a	29.1 (±11.4)	n/a	27.9 (±13.1)	30.3 (±9.8)	p=0.55
UPDRS motor score OFF	n/a	n/a	36.0 (±10.4)	n/a	32.8 (±11.3)	39.1 (±8.7)	p=0.07
Change in motor score	n/a	n/a	6.9 (±8.0)	n/a	4.8 (±7.8)	8.8 (±8.0)	p=0.14
Levodopa equivalent dose (mg/24 hours)	n/a	n/a	621 (±356)	n/a	534 (±339)	702 (±363)	p=0.17
Hours since last dose – OFF	n/a	n/a	18 (±3)	n/a	19 (±3)	17 (±3)	p=0.07
Hours since last dose – ON	n/a	n/a	2.3 (±1.5)	n/a	2.7 (±1.6)	1.8((±1.5)	p=0.11
Depression (BDI-II)	n/a	3.9 (±3.9)	14.5 (±7.9)	**p<0.0001**	11.3 (±7.0)	17.4 (±7.7)	**p=0.02**
Dysphoria sub-scale	n/a	(1.2±1.6)	(5.0±4.1)	**p<0.0001**	(4.5±4.1)	(5.6±4.1)	p=0.43
Global Cognition (ACE)	97.5 (±2.9)	95.7 (±3.7)	90.7 (±8.2)	**p=0.004**	93.5 (±5.1)	88.2 (±9.8)	p=0.06
Digit span	19.4 (±3.8)	21.2 (±4.5)	17.1 (±3.6)	**p=0.0002**	16.7 (±3.1)	17.5(±4.1)	p=0.57

Table 6-1. Participant demographics for experiment one and two. *LARS – Lille apathy rating scale; UPDRS – Unified Parkinson's disease rating scale; BDI-II – Beck's depression inventory II; ACE – Addenbrooke's cognitive examination III; ^chi-squared test; (all values are mean +/- standard deviation)*

6.3.3 Decision making Paradigm

Participants undertook the same task described in **Chapter 5, experiment three** (**Figure 6-1**). Briefly, participants were seated in front of a desktop computer running Psychtoolbox, implemented in MATLAB (MathWorks USA). Their task was to decide when to leave their current setting (patch), in which they were earning exponentially decrementing rewards over time, to move to a new patch, so as to maximise their overall reward gain. Moving on incurred a fixed time delay, during which they could not gather any reward. Participants were aware that they had only a fixed amount of time for the experiment, but that there were a potentially unlimited number of patches. There were three patch-types – high, medium and low – varied by the scaling factor of the reward function. There were two independent background environments. In the rich environment (signalled to participants by a gold border on the screen), 50% of encountered patches were high-yielding, 30% medium-yield and only 20% low-yielding. Conversely in the poor environment 50% of encountered patches were low-yielding, 30% medium-yield and only 20% high-yielding. Therefore, the background reward rate was lower in the poor environment, meaning that in this environment participants should leave all patch-types later than in the rich environment if behaving optimally **(Figure 1-5).** Whilst background reward rate depended on the distribution of patch-types within each environment, foreground reward rate (after T seconds in a patch) was determined by the equation:

$$g'(T) = S * e^{-0.075*T}$$

Here, the three possible values (32.5, 45 or 57.5) of the scaling factor S determined whether a patch was low, medium or high yielding. The height of milk displayed in the bucket on-screen was proportional to the integral of this function between time = 0 and T and was updated at a frequency of 20Hz.

Thus, foreground (patch-type) and background (farm-type) reward rates were independently manipulated, allowing the effects of both dopamine and apathy on each of these features to be assessed.

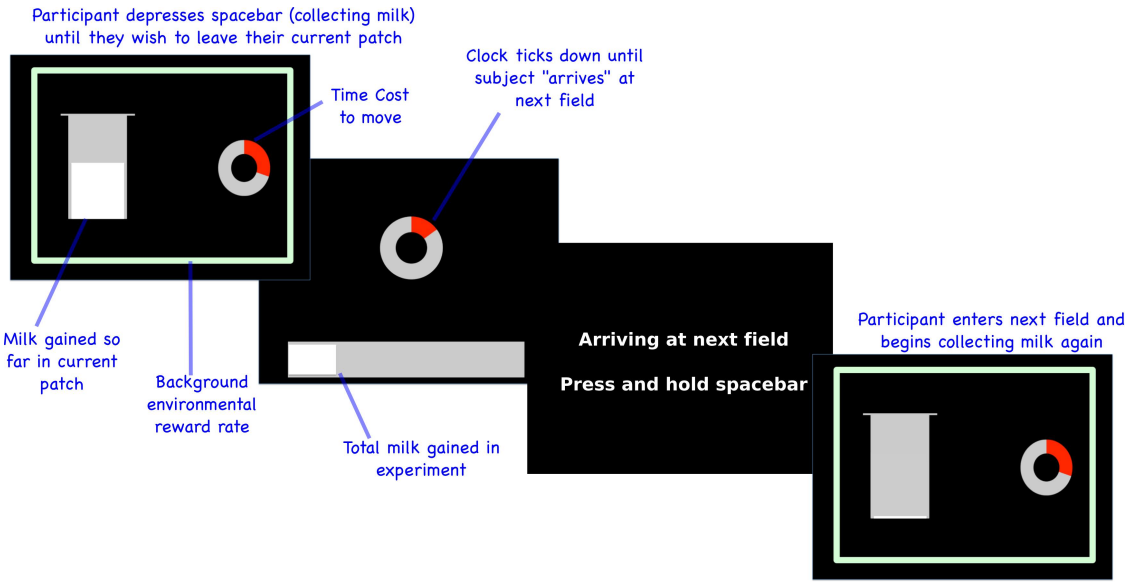


Figure 6-1. Patch leaving task manipulating foreground and background reward rates

The task was framed as a milk-gathering task. Participants spent an equal amount of time (10minutes) in each of two farms, which were composed of fields containing cows (the patches). When in a field participants automatically received milk, displayed on screen as a grey bucket continuously filling up. The rate of filling exponentially decreased over time. The scale of filling was determined by the patch-type (low, medium or high), and described to participants as equivalent to the number of cows in that field. Participants moved on from a field by releasing the spacebar (which they had been cued to depress at the onset of the trial). The screen display then changed to show a clock ticking down the seconds until they reached the next field as well as the total milk harvested so far in the experiment. One second before the start of the next patch, participants were cued to press and hold down the spacebar, and they then moved automatically into the next field and began collecting milk. The current farm environment (poor or rich) was continuously displayed by a coloured border on the screen (rich = gold, poor = green). Conversely, participants were not given explicit information about the current patch-type, but instead had to deduce this by watching the rate of filling of the milk bucket. Participants were aware they had approximately 10 minutes in each farm-type, but were not shown any cues to indicate how much time had elapsed.

6.3.4 Statistical methods

The primary analysis for both Experiment ONE and TWO was conducted using a hierarchical linear mixed effects model (*fitlme* in MATLAB, Mathworks) to account for between and within subject effects. All fixed effects of interest (patch, environment,

dopamine and, in experiment two, apathy) and their interactions were included, and the inclusion of random effects was determined by recommended methods (Barr et al., 2013), to reduce the likelihood of type one errors. The final model was selected based on minimisation of the Bayesian information criterion (BIC).

Experiment ONE:

$$Leaving\ Time = 1 + patch * env * DA + (1|sub) + (1|sub:DA) + (1|sub:patch) + (1|sub:env) + (1|sub:patch:env:DA)$$

Experiment TWO:

$$Leaving\ Time = 1 + patch * env * DA * Ap + (1|sub) + (1|sub:DA) + (1|sub:patch) + (1|sub:env) + (1|sub:patch:env:DA)$$

patch = foreground reward rate, env = background reward rate, DA = dopamine state, Ap = Apathy status sub = subject. Fixed effects are shown in blue, random effects in green.

Notably the reported effects in both these models were also present in the simpler models fitting only a random effect of subject.

To avoid the potentially biasing effects of outlying data points on the primary analysis, I excluded, subject by subject, any trials in which the leaving time was more than 3 standard deviations above that individual's mean leaving time. Of note, this approach did not change the significance (or otherwise) of any reported results compared to analysis of the full data set.

6.4 Results

6.4.1 EXPERIMENT ONE

Healthy human foragers are guided by MVT principles

MVT predicts that foreground and background reward rates should both impact on leaving times, but that these two effects should be independent (**Figure 6-2 a & b**). Using the LME on leaving times (see methods) I indeed found a main effect of foreground reward, a main effect of background reward, but no interaction. (Foreground: $F(1,57)=425$, $p<0.0001$; Background: $F(1,28)=16.9$, $p=0.0003$; Foreground * Background: $F(1,197)=0.03$, $p=0.86$ **Table 6-2**). Moreover, participants' behaviour (in the placebo condition) conformed to the predicted directionality of these

effects, both leaving patches later when yield was higher and later when in the poor environment (**Figure 6-2 c & d**).

Although participants showed effects in the direction predicted by MVT, all participants showed a significant bias to remain in all patch-types and in both environments longer than optimal; mean deviation from predicted leaving time 8.2s ± 0.7s, t_{28} = -11.2, p<0.0001, (**Figure 6-2 e & f**). However, it has been noted that non-human primates also show a bias to stay (Hayden et al., 2011), but are close to optimal once controlling for this bias. Strikingly, subtracting each participant's mean leaving time to look at the magnitude of the effect of background (poor-rich leaving time) and foreground (high-low yield), participants were not significantly different from optimal changes between environments (t_{28}=0.29, p=0.77**, Figure 6-2d**). There was however a trend towards a significant difference associated with changes in foreground environment, with participants tending to leave high yield patches later than would be predicted by an optimal foraging agent (t_{28}=2.02, p=0.053 **Figure 6-2c**).

Thus, participants in the baseline (placebo) condition were close to optimal in terms of the effects of the background environment, but did show a general bias to remain in patches longer.

Table 6-2. Hierarchical linear mixed effects model – Experiment one

	PE	T stat	F stat	DF*	P
Patch	**3.63**	**20.6**	**425**	**57.3**	**<0.00001**
Env	**0.76**	**4.1**	**16.9**	**28.1**	**0.0003**
Drug	-0.34	-1.37	1.86	29.3	0.18
Env*Drug	**-0.18**	**-2.29**	**5.22**	**200.1**	**0.023**
P * E	0.01	0.17	0.03	197.1	0.86
P * D	-0.09	-1.14	1.29	186.6	0.26
P * E * D	-0.04	-0.56	0.31	186.4	0.58

* DF were calculated using the Satterthwaite correction method.

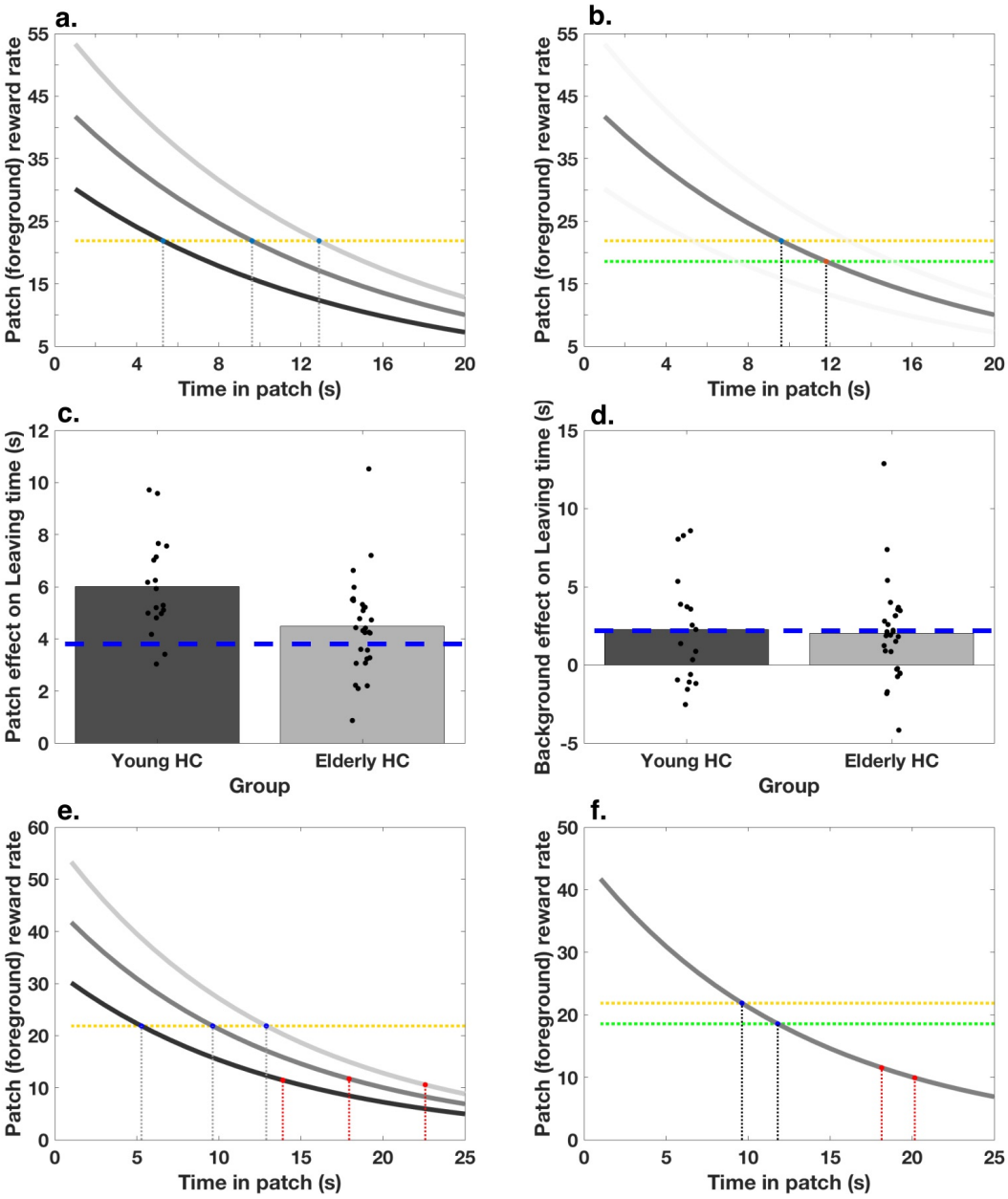


Figure 6-2. Healthy human foragers are sensitive to predictions of MVT

(**a**) The optimal leaving time from each patch occurs when the instantaneous patch reward rate is equal to the background average reward rate in the environment (yellow dashed line), and is shown for each of the 3 patch-types (in the rich environment). (**b**) In the poor environment (green dashed line) the background average reward rate is lower, and therefore the optimal patch leaving time is later (red dot compared to blue dot in rich environment). (**c**) Both young and elderly participants were sensitive to the effect of changing foreground reward rate (patch-type), leaving patches later as patch-yield improved. (**d**) Both young and elderly controls were sensitive to the effects of changing background reward rate, leaving all patch-types later in poor compared to rich environments. Furthermore, the magnitude of these effects was close to that predicted by the MVT (blue dashed lines). Both groups showed a bias to remain in patches longer than predicted, independent of the effects of foreground (**e**) or background (**f**) reward rate – elderly participant data is shown, with red dots corresponding to leaving times in each patch-type (**e**), and each environment (**f**).

Cabergoline effects in healthy participants

There was a significant interaction between drug condition and the effect of background reward rate on leaving time ($F(1,200)=5.22$, $p = 0.023$). Although the effect of background environment was significant both ON and OFF cabergoline, the magnitude of this effect was reduced in the ON compared to OFF condition (**Figure 6-3 a & b**). In turn, this change was mainly due to participants leaving patches earlier ON cabergoline when the background environment was *poor (*mean difference = 1.16s $\pm$ 0.67s, $t_{28}=1.75$, $p=0.09$; **Figure 6-3c)**. This effect is consistent with participants estimating the background reward rate (in poor environments) as higher when ON drug compared to OFF. When the background environment was rich, leaving times were similar between drug and placebo conditions (md = 0.3s $\pm$ 0.5s, $t_{28}=0.59$, $p=0.56$).

There was no significant drug * patch interaction ($F(1,187)=1.29$, $p=0.26$), meaning that cabergoline did not change the way participants used foreground (patch) reward rate information to guide leaving decisions (**Figure 6-3 d & e**). There was also no statistically significant difference in leaving times overall on drug compared to placebo (md=0.73s, $F(1,29)=1.86$, $p=0.18$) and the observed drug * environment interaction was present across all patch types, with no 3-way interaction ($F(1,186)=0.31$, $p=0.58$).

Therefore cabergoline exerted a specific, rather than general effect on patch leaving behaviour, altering only the influence of background reward rate on leaving time.

Summary

Cabergoline altered the influence of background, but not foreground, reward rate on patch leaving time in a healthy elderly population. Baseline performance in this group of older people was very similar to younger people, with participants demonstrating predicted sensitivity to variables specified in the MVT.

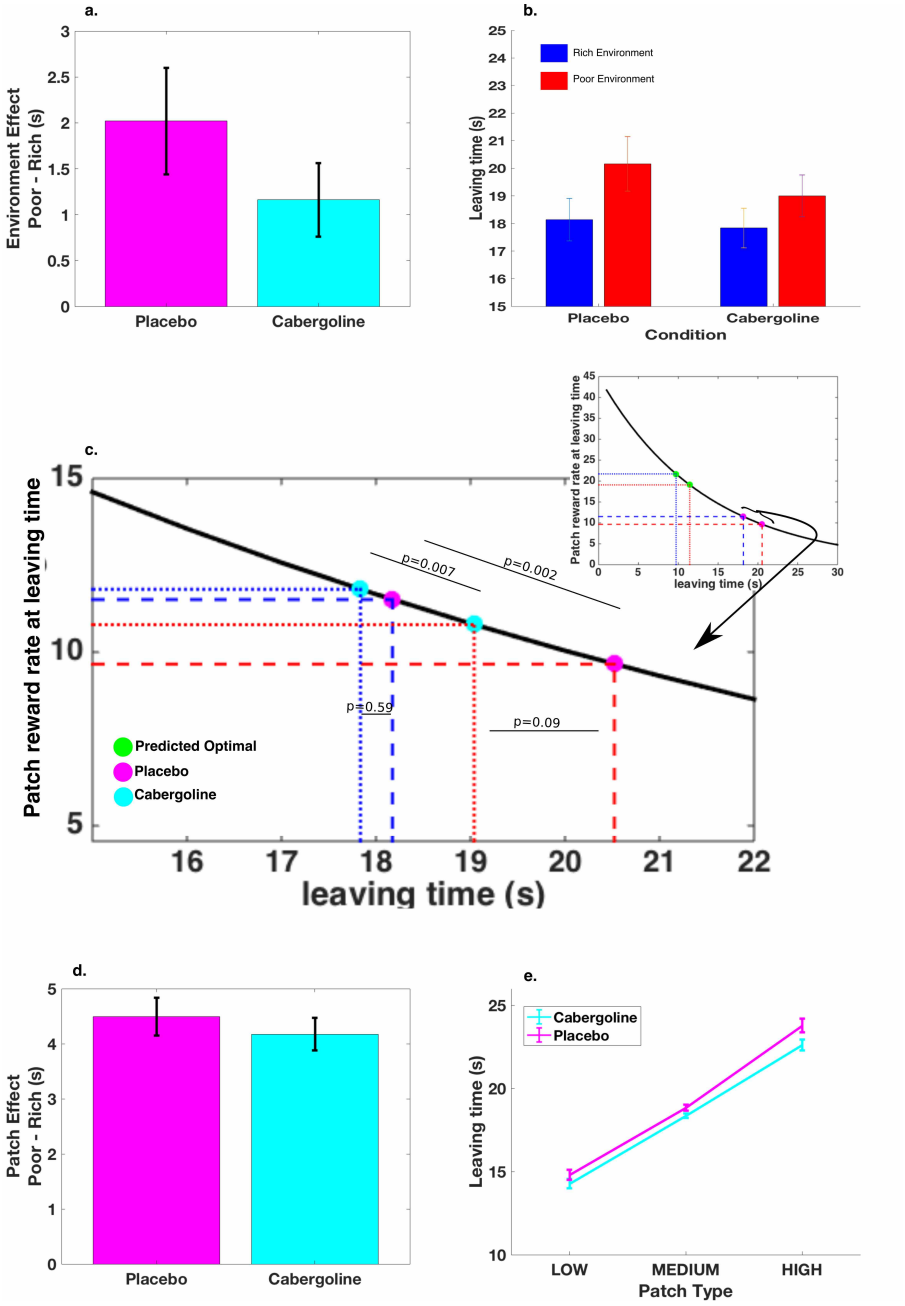


Figure 6-3. Cabergoline changed the effect of background environment on patch leaving behaviour

(**a & b**) There was a significant interaction between drug and background reward rate on leaving time, with a reduced effect of background environment ON cabergoline compared to OFF (p=0.023). (**c**) In turn, this was mainly driven by participants ON cabergoline *leaving patches earlier – and therefore when the patch reward rate was higher – in poor environments*. The panel inset shows the mean patch reward rate (y axis) at patch leaving time (x axis) for the placebo condition (magenta dots) and the predicted optimal (green dots). The main panel zooms in on the relevant period of leaving times to illustrate the effects of changing background environment (dashed lines; BLUE: Rich environment, RED: Poor) in placebo (magenta dots) and cabergoline (cyan dots) conditions. (**d**) There was no significant interaction between drug and foreground reward rate effect on patch leaving (p=0.26). (**e**) There was no main effect of cabergoline on raw leaving times (p=0.18).

6.4.2 EXPERIMENT TWO

Background environment, dopamine and motivational state

There was a significant 3-way interaction between environment, dopamine and apathy ($F(1,200)=7.03$, $p=0.0086$ **Table 6-3**). The OFF state was associated with a *reversal* of the expected effect of background environment on patch leaving time, however *this effect was dependent on apathy.* That is, apathetic PD patients OFF medications remained in patches for longer when background environment was *rich* compared to *poor*. Dopamine (ON state) restored the behaviour of these patients to the predicted direction of effect, leaving patches later when background environment was *poorer* (Change in Environmental effect ON-OFF: $t_{17}=2.24$, $p=0.038$). In contrast, dopamine did not alter the effect of environment on patch leaving time in non-apathetic patients (Change in Environmental effect ON-OFF: $t_{16}=0.31$, $p=0.76$). Therefore, the observed change in background environment effect on patch leaving, ON and OFF dopaminergic medications, was driven by the apathetic group (**Figure 6-4a**).

In this PD group, background environment alone did not have a significant main effect on patch leaving time ($F(1,35)=1.21$, $p=0.28$), rather its effects depended on both drug and motivational state.

Foreground reward, dopamine and apathy

As in the healthy control population, foreground (patch) reward rate strongly predicted leaving times ($F(1,68)=252$, $p < 0.0001$, **Table 6-3**). However, neither change in dopamine state or baseline motivation affected the degree this variable influenced patch leaving behaviour (patch*DA: $F(1,188)=1.02$, $p=0.31$; patch*Ap: $F(1,68)=2.26$, $p=0.14$). The magnitude of the patch effect was however reduced as a function of disease, with PD patients – whether ON or OFF their dopaminergic drugs – showing reduced sensitivity to this metric compared to HCs, (**Figure 6-4b)**. Mean patch effect: HC=4.4s, PD-ON=3.3s, PD-OFF=2.9s; one-way ANOVA (group effect) $F(2,96)=7.41$, $p=0.001$. Post-hoc t-tests: HC vs PD-ON: MD=1.1s, $t=2.48$, $p=0.016$; HC vs PD-OFF: MD=1.5s, $t=4.12$, $p=0.0001$; PD-ON vs PD-OFF: MD=0.38s, $t=1.06$, $p=0.29$).

Effect of Parkinson's disease, apathy and dopamine on raw patch leaving times

Neither dopamine nor apathy had independent main effects on patch leaving time ($F(1,35)=0.09$, $p=0.77$ & $F(1,35)=0.12$, $p=0.73$ respectively, Figure 6-4c). There was also no two-way interaction between dopamine and motivational state ($F(1,35)=0.003$, $p=0.96$), nor were other two-way, three-way or the full four-way interaction significant, **Table 6-3**.

Table 6-3. Hierarchical Linear Mixed Effects Model – Experiment two

	PE	T stat	F stat	DF	P
Patch	**2.71**	**15.9**	**252**	**68**	**<0.0001**
Env	-0.30	-1.10	1.21	34.5	0.28
DA	-0.16	-0.29	0.09	34.8	0.77
Apathy	0.44	0.35	0.12	35	0.73
Patch*Env	0.01	0.10	0.01	198.6	0.92
Patch*DA	-0.11	-1.01	1.02	188.4	0.31
Env*DA	0.002	0.02	<0.001	199.6	0.99
Patch*Ap	-0.36	-1.5	2.26	67.6	0.14
Env*Ap	0.01	0.37	0.07	34.4	0.80
DA*Ap	-0.04	-0.05	0.003	34.8	0.96
Pa*Env*DA	-0.008	-0.08	0.006	188.6	0.94
Pa*Env*Ap	-0.11	-0.79	0.62	196.9	0.43
Pa*DA*Ap	0.08	0.55	0.30	190.0	0.58
Env*DA*Ap	**-0.38**	**-2.65**	**7.03**	**200.4**	**0.0086**
P*Env*DA*Ap	<0.001	0.002	<0.001	189.5	1.0

* DF were calculated using the Satterthwaite correction method.

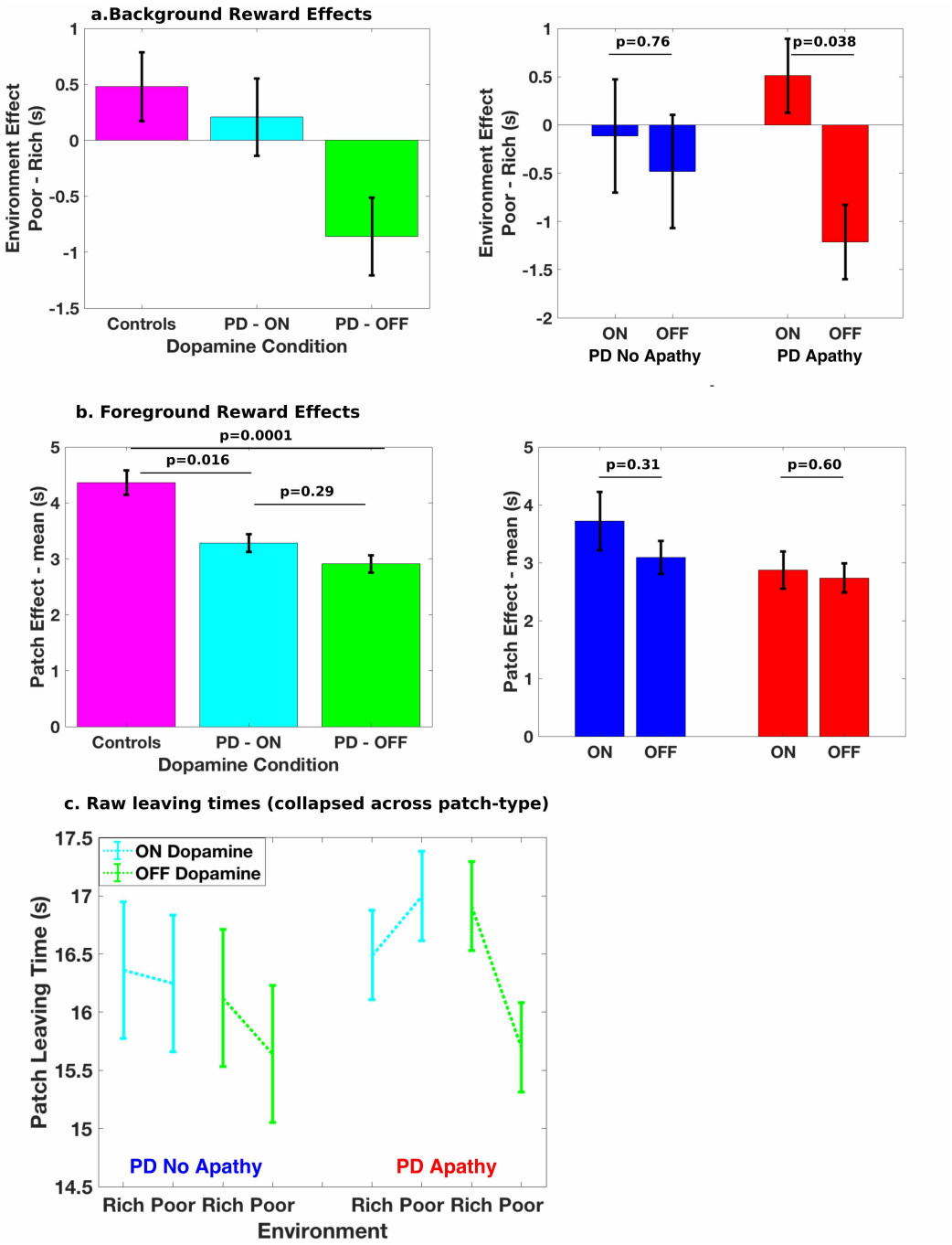


Figure 6-4. Apathy, dopamine and background reward rate interact during patch leaving decisions in PD

(**a**) There was a significant interaction between background reward rate, dopamine and apathy (p=0.0086). Dopamine changed the influence of background reward environment on patch leaving, but only in the patients with apathy. (**b**) There was no interaction between dopamine, apathy and the influence of foreground reward rate on patch leaving (p=0.58). PD was associated with a reduced effect of foreground reward rate on leaving time, independent of dopamine condition and apathy status. (**c**) There was no main effect of dopamine or apathy on leaving time. Here, raw leaving times in each environment (rich and poor), collapsed across patch-type, are shown for non-apathetic and apathetic PD patients, in the ON and OFF states.

Summary

Dopamine changed the influence of background, but not foreground, reward rate on patch leaving behaviour, but only in those PD patients who were apathetic. Neither apathy nor dopamine had a general effect on patch leaving behaviour – rather their effect was limited to the influence of a specific reward property – background reward context.

6.4.3 Additional control analyses: Experiments ONE and TWO

Session and Order effects

In both experiments ONE and TWO, the inclusion of session (1st or 2nd) worsened model fit (change in BIC 7.6 and 8.2 respectively), and session effect was not significant (Expt ONE: PE=-0.16, $F(1,29)=0.36$, $p = 0.56$; Expt TWO: PE=0.12, $F(1,35)=0.09$, $p = 0.77$). Similarly, including order (the session * drug interaction) also worsened model fit (change in BIC 14.2 and 16.1 respectively) and again this term was not significant (Expt ONE: PE=0.87, $F(1,29)=1.4$, $p = 0.25$; Expt TWO: PE=-0.36, $F(1,35)=0.3$ $p = 0.59$). Therefore session and order effects were not included in either final model. The inclusion of these effects did not change the significance (or otherwise) of the other model terms.

Variance of patch leaving times

Variability in leaving times within each participant provides a metric of consistency, and thus how much each person was attending to the experimental task. There was no difference in the variance of patch leaving times between controls, and non-apathetic and apathetic Parkinson's disease patients; One-way ANOVA: $F(2,61)=1.1$, $p=0.34$, (**Figure 6-5 – left panel**). Similarly, variance of leaving time did not change significantly with dopamine state, either in the Parkinson's disease or the healthy elderly groups ($MD_{\mathbf{ON\text{-}OFF}} = 0.25$, $t_{34}=1.25$, $p=0.22$; $MD_{\mathbf{PLAC\text{-}CAB}} = 0.31$, $t_{28}=1.34$, $p=0.19$, **Figure 6-5 – centre and right panel**). This suggests that neither changes in dopamine, nor apathy state had a significant influence on a person's general attention to the task.

Other potential confounders

Possible confounding influences of participant weight, height, BMI on the dopaminergic effect were investigated further. There were no significant correlations between these variables and the dopamine effect (all $p > 0.1$). Therefore they were not included in the final model. The inclusion or exclusion of these terms did not change the significance of any reported effects.

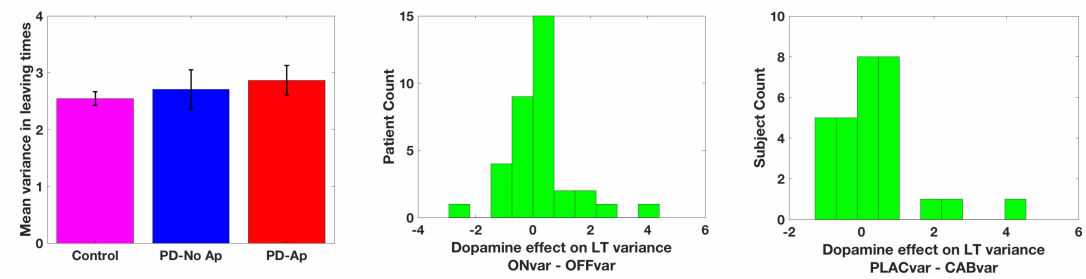


Figure 6-5. Variance of leaving time decisions did not change significantly between groups

There was no effect of either apathy state (**left panel**) or dopamine state (**centre** (expt 2) and **right** (expt 1) panels) on each participant's variance in patch leaving times.

6.5 Discussion

In these two separate studies, changes in dopaminergic tone altered the influence of background environmental reward rate on patch leaving behaviour in humans. Furthermore, in PD this effect was modulated by the presence of apathy. The same effects of dopamine were not observed on foreground reward rate, nor did either dopamine or apathy cause a general change in patch leaving behaviour. Rather, it was the specific interplay between dopamine, apathy and background reward rate that drove the observed changes. These results link tonic dopamine levels to processing of background reward information. Furthermore they reveal a mechanism by which changes in dopaminergic functioning could lead to neurobehavioural syndromes such as apathy. Specifically, they suggest that the altered reward sensitivity previously demonstrated in apathetic PD patients may – at least in part – be linked to difficulty utilising information about the background reward environment – a process for which the dopaminergic system seems crucial.

The results provide new evidence for the role of tonic dopamine in decision making. In both studies, consistent with my hypothesis, changes in dopamine state altered the influence of background reward information on patch leaving behaviour (albeit with the additional influence of apathy in the second study). The drug manipulation is assumed to alter tonic dopamine levels, a component of the dopaminergic neuromodulatory system which has been ascribed a crucial, although at times controversial, role in signalling background reward rates (Hamid et al., 2016; Niv et al., 2007; Zenon et al., 2016). Although some existing evidence suggests tonic dopamine levels encode information about background reward rate, and therefore the opportunity cost of actions (Guitart-Masip et al., 2014; Niv et al., 2007), other authors have argued it encodes a more specific signal for the value of a current action, independent of environmental context (Zenon et al., 2016).

The current study supports the view that dopamine encodes information about background reward rate and therefore the environmental reward context. In both experiments, manipulating tonic dopamine levels specifically altered the influence of background reward rate on patch leaving decisions. Furthermore, in the first experiment in which participants were tested ON and OFF the D2 agonist cabergoline, this result was mainly driven by participants leaving patches in poor environments *earlier* when ON drug compared to OFF. This behaviour is consistent with participants estimating background reward rates (in poor environments) *higher* ON cabergoline, the predicted effect of an increase in tonic dopamine levels. Put another way, ON cabergoline, participants behaved as if the opportunity cost associated with remaining in patches within the poor environment was higher. Similarly in the second experiment, dopamine administration in apathetic patients restored the effect of background reward information on patch leaving behaviour to the predicted direction. That is, dopamine changed the behaviour of these patients towards adaptive use of environmental reward context. It should be noted however that the Cabergoline manipulation theoretically could have increased, or decreased tonic dopaminergic activity. This is because cabergoline binds to both post and pre-synaptic D2 receptors with opposing effects. Binding to pre-synaptic autoreceptors reduces phasic dopamine release and tone (Chen et al., 2005; Grace, 1991; Pizzagalli et al., 2008), whilst post-synaptic receptor stimulation increases dopaminergic tone (Brooks et al., 1998). Therefore, although the

dopaminergic manipulation was specifically associated with changes in use of background reward information, caution should be exercised in further interpreting this result.

Dopamine state, in both healthy participants and those with PD, did not alter the use of foreground (patch) reward information to guide leaving time decisions. An abundance of evidence links dopamine to the processing of rewarding outcomes, encoding the value of potential actions and motivating behaviours towards goals (Hamid et al., 2016; Howe et al., 2013; Kurniawan et al., 2011; Le Bouc et al., 2016; Salamone and Correa, 2012; Schultz, 2007; Syed et al., 2016). The paradigms used in the above studies have generally focussed on reward along a single axis and decisions about whether to exert effort to pursue a rewarding goal, rather than presenting foraging-type problems where foreground and background elements must be contrasted. The current work suggests dopamine has a less important role in utilising information about what you are already doing, in contradistinction to what you could do (Hamid et al., 2016; Syed et al., 2016), what you have done (Schultz, 2007) and the reward context in which your current behaviours are occurring (the current study).

The effect of background environmental reward rate on patch leaving decisions varied significantly in apathetic – but not non-apathetic – PD patients as a function of dopaminergic tone. In the OFF state, apathetic patients showed a *reversal* of the predicted effect of background reward rate (Stephens and Krebs, 1986), persisting in patches for longer when environmental reward rates were higher. This behaviour is not consistent with patients simply estimating environment reward rate as lower, but rather suggests a failure to utilise available information specifically about background reward context to appropriately guide decisions.

Consistent with the main hypotheses of this study, dopamine restored apathetic (but not non-apathetic) patients' behaviour to the predicted direction (leaving patches earlier in rich compared to poor environments). Previous work has implicated disrupted reward systems in PD apathy (Lawrence et al., 2011; Le Heron et al., 2018; Martinez-Horta et al., 2014a; Muhammed et al., 2016), but these studies have not distinguished between different aspects of reward information. The effects seen in the current study offer a more nuanced interpretation of the relationship between reward and apathy.

Specifically, apathetic patients used background reward information mal-adaptively to guide patch leaving decisions, dependent on baseline dopamine levels. This result is consistent with the hypothesis that disrupted representation of the background reward environment contributes to apathy in PD, whilst suggesting a potential role for dopamine in ameliorating this deficit.

The interaction between background reward rate, apathy and dopamine contrasts with other recent findings on reward and apathy in PD, in which apathy was associated with blunted physiological (Muhammed et al., 2016) and behavioural (Le Heron et al., 2018) responses to reward irrespective of baseline dopaminergic state. Together these results suggest that reward processing can be altered in apathy along more than one mechanistic axis. While apathy is associated with a blunting of the normal incentivising effects of reward – possibly in a dopamine-independent manner – the current study demonstrates it is also associated with changes in utilising information about reward context to guide choice, dependent on dopaminergic tone. This demonstrates another component of effort-based decision making which may be disrupted in apathy and fits with previous reports linking apathy and dopaminergic denervation (Santangelo et al., 2015; Thobois et al., 2010).

PD itself was associated with a reduced effect of foreground reward, across both dopamine and apathy state. This is consistent with previous work demonstrating reduced reward sensitivity in PD patients (Manohar and Husain, 2015), and may be a more general feature of the disease. It is however difficult to disentangle whether this PD effect is related to or independent from the dopaminergic system. PD is characterised by dysfunction within dopaminergic systems (Kalia and Lang, 2015), dysfunction that is not entirely reversed by administration of dopaminergic medications which could therefore limit the effects of drug. Furthermore, it is now clear that many other neuromodulatory systems (including serotonergic, cholinergic and noradrenergic) are affected in PD, systems which have also been liked to reward processing and motivating behaviours towards rewards (Salamone et al., 2016).

It is important to consider more trivial explanations for the findings in these studies, such as reduced attention to the task in the OFF state. This however is unlikely in my opinion because of the specific, rather than general changes in behaviour associated

with both the drug manipulation, and apathy state. Furthermore a control analysis demonstrated no difference in *variance* of patch leaving times associated with either of these factors, suggesting that in all conditions participants were appropriately attending to the task. The results could not be explained by either session (1st or 2nd) or order (ON-OFF or OFF-ON) effects, with the inclusion of either of these variables worsening model fit and leaving other findings unchanged. Finally, the presence of a robust dopamine effect associated with the same variable (background reward rate) across two independent experiments strengthens the reliability of the results. It will however be important to test the same paradigm in an apathetic group in which the dopaminergic system is not thought to be primarily affected, to better understand how these findings may relate to apathy more generally.

The results of these experiments demonstrate the utility of conceptualising human decision making within a foreground/background foraging framework. The two experiments presented in this chapter reveal a specific association between dopamine, apathy and the use of reward information to guide patch leaving decisions. Changes in dopamine levels affected the influence of background reward context on switching behaviour, consistent with a crucial role for tonic dopamine in representing background reward rates. Apathy was associated with changes in the processing of this same background information, dependent on dopamine levels. This extends our understanding of the disrupted reward processing that has been associated with apathy, bringing us closer to a mechanistic understanding of this debilitating condition.

7 General Discussion

I have investigated whether apathy – a disorder of motivation manifesting as a reduction in goal directed behaviours – is caused by disruption of the brain mechanisms that underpin effort-based decision making. Specifically, I tested the general hypothesis that apathy occurs because of changes in the way that patients with brain disorders weigh up the costs of making an action against the rewarding outcomes of that action. The main finding, presented in **chapters 2, 3 and 4** – that apathetic patients show reduced incentivisation by rewards – informed the subsequent general hypothesis presented and tested in **chapters 5 and 6** – that apathy may be usefully considered a disorder of patch leaving behaviour, and relate to deficits in integrating information about the background reward environment to drive choice. These results provide a more nuanced account of the deficit in reward processing associated with apathy, whilst, in combination with **chapter 4**, further delineate the ways in which apathy overlaps with, and is dissociated from, the mesolimbic dopaminergic system. In the following pages I present a brief summary of the main findings presented in each of the empirical chapters. I then discuss the clinical and scientific implications of these findings for our understanding of apathy, emphasizing important future directions of research in the area.

7.1 Summary of Experimental Findings

7.1.1 Chapter TWO

In this chapter I tested whether apathy was associated with altered effort-based decision making in patients with CADASIL, an autosomal dominant genetic model of small vessel disease (SVD). 19 patients, 11 of whom were clinically apathetic, as well as age and gender matched controls completed a computer-based effort-based decision making task in which they were presented with sequential offers of reward ('apples' with a monetary value) in return for exerting physical effort (on a hand-held dynamometer). They accepted or rejected each offer based on whether they felt *it was worth* exerting the required effort for the offered reward, and over the experiment effort and reward were manipulated such that each participant received offers from an evenly sampled

'decision space' (**Figure 2-1**). Apathetic CADASIL patients rejected more offers than non-apathetic patients and controls, whilst importantly patients without apathy did not differ from the control group (**Figure 2-4**). Crucially, this change in responding associated with apathy was not global across the sampled decision space, but was driven by a subset of offers – *those in which the rewarding outcome was low*. Conversely, apathetic patients were prepared to exert as much effort as non-apathetic patients and controls – even at the highest effort levels – if the rewarding outcomes were high (**Figure 2-5**).

That apathetic behaviour was driven by reduced incentivisation by the rewarding outcomes of actions rather than the action costs themselves, was demonstrated using two complimentary analysis techniques: a simple RM-ANOVA and a computational model of choice (**Figure 2-5**). Apathetic CADASIL patients were also significantly slower than non-apathetic patients and controls to decide whether to accept or reject an offer, but importantly still showed expected variations in decision time with choice difficulty suggesting this result was not simply related to attention (**Figure 2-6**). Furthermore there were no significant difference in non-task related measures of processing speed, suggesting the slowed decision making associated with apathy may be a specific rather than general phenomenon.

Apathy in this study was associated with a significantly reduced quality of life, underlining the broader importance of this entity for patient well-being. In summary, this experiment demonstrated that effort-based decision making is disrupted in apathetic CADASIL patients, in a specific rather than global manner. It suggests that the phenotype of apathy in everyday life – a reduction of goal directed behaviour – occurs because patients no longer attain sufficient drive from the options in their environment, rather than the barrier of the effort costs of behaviours.

7.1.2 Chapter THREE

The previous chapter demonstrated a behavioural association between apathy and reduced incentivisation by rewards. In this chapter I investigated whether apathy in these same CADASIL patients was also associated with physiological markers of

reduced reward sensitivity and anatomical changes consistent with these findings. To objectively measure each participant's sensitivity to rewards I used a previously validated eye-tracking task (**Figure 3-1**), and recorded the degree to which people's pupils dilated as they were presented with stimuli signalling the potential rewards available on the current trial. The normal reward-related response – greater dilatation with greater rewards – was present in the control group and non-apathetic CADASIL patients, but significantly blunted in the apathy group, despite equivalent baseline pupil size.

Furthermore, this autonomic measure of reward sensitivity was significantly correlated with the behavioural measure of reward sensitivity derived in the previous chapter (**Figure 3-2**). That is, apathetic CADASIL patients showed reduced incentivisation by the rewarding outcomes of their actions on the decision-making task, and this behavioural reduced sensitivity to rewards correlated with a physiological measure of reward sensitivity – pupillary dilatation to rewards. Interestingly, even though apathetic patients showed a diminished autonomic response to reward information, when externally cued to saccade to a rewarding target their response velocity did not differ from non-apathetic patients or controls (**Figure 3-3**).

In the second part of this chapter I investigated whether disruption of axonal integrity within white matter tracts – the core site of pathology in CADASIL – was associated with apathy. Specifically, I hypothesised that there would be changes within white matter regions connecting neural areas crucial for effort-based decision making – including medial frontal cortex and ventral striatum – and that these changes would relate to individual measures of reward sensitivity. Using a tract-based spatial statistics analysis I found that apathy was associated with reduced fractional anisotropy (FA) of white matter fibres within specific white matter regions, including anterior cingulum, white matter associated with OFC and anterior cingulate, the body of the corpus callosum and the anterior limb of the internal capsule (**Figure 3-4)**. Importantly there was no difference between apathetic and non-apathetic groups in mean FA (across the whole skeleton), or total volume of white matter hyperintensities (**Figure 3-6 & Figure** 3-8). Furthermore, FA values for non-apathetic CADASIL patients overlapped significantly with healthy controls within the areas associated with apathy (**Figure 3-5**).

Additionally, just as the choice reward sensitivity parameter correlated with autonomic responses to reward, so too did it correlate with the FA values in most of these apathy associated areas (**Figure 3-7**). Together, the results of this chapter provide physiological evidence of insensitivity to rewards in CADASIL associated apathy, and anatomical evidence strengthening the behavioural results of disrupted effort-based decision making underlying the apathetic syndrome.

7.1.3 Chapter FOUR

In this chapter, using the same behavioural paradigm as in chapter two, I investigated whether disrupted effort-based decision making was associated with apathy occurring in the setting of a different neurological disorder – Parkinson's disease (PD). Furthermore, by testing 39 patients ON and OFF their normal dopaminergic medications, I explored whether changes in decision making associated with apathy were modulated by the neurotransmitter dopamine – a crucial component of reward processing and motivated behaviour that had previously been implicated in PD apathy. I found that apathetic PD patients also rejected more offers than non-apathetic patients or controls, and that – just as in the CADASIL group – this change was mainly driven by reduced acceptance of low reward outcome offers.

Dopamine depletion was also associated with a reduced acceptance rate (**Figure 4-3**). Intriguingly, apathy and dopamine depletion affected dissociable regions of the sampled decision space. Whilst apathy was characterised by reduced responses to predominantly low reward offers, the effect of dopamine depletion on choice manifested as a reduced acceptance of predominantly high effort, high reward offers (**Figure 4-4**). This meant that PD patients accepted more high effort, high reward offers ON compared to OFF their dopaminergic medications, irrespective of their underlying motivational state.

I also investigated the effects of apathy and dopamine depletion on response vigour – indexed by the overshoot of the motor response to the target force level. As with the choice data, apathy and dopamine had dissociable effects. Whilst being ON dopamine medications was associated with more vigorous motor responses (despite this metric

being uncoupled from reward), apathy was not associated with any change in this metric. That is, once apathetic patients decided to accept an offer, the vigour of their response was the same as for non-apathetic patients (**Figure 4-5**).

Finally, I tested for differences in decision time associated with apathetic and dopaminergic states. There was no statistically significant change in decision time associated with apathy, however the OFF state was associated with a trend towards *faster* decisions across the sampled decision space, an observation that merits further study (**Figure 4-6**). As with the CADASIL group, apathy in PD was associated with a significantly worse quality of life.

In sum, this chapter demonstrated clear alterations in effort-based decision making associated with apathy in PD, driven, as with the CADASIL patients, by reduced incentivisation by rewarding outcomes rather hypersensitivity to the costs of actions themselves. Furthermore, these changes were dissociable from the effects of dopamine depletion on both choice and motor response. This suggests that apathy occurring in the context of PD is unlikely to be explained by a dopaminergic deficit alone, highlighting the importance of considering other neuromodulatory systems as both explanatory factors and therapeutic targets.

7.1.4 Chapter FIVE

In this chapter, in order to further explore the mechanisms underlying apathy I shifted my emphasis from a binary (accept/reject) decision making paradigm to a task structure that emphasised decisions based on a comparison between foreground (patch) and background (environment) characteristics. This class of decision making problem – often termed the patch leaving problem – has likely been a ubiquitous feature of the environmental milieu influencing neural development throughout evolutionary history. However very little is known about whether the theories – such as the marginal value theorem – that effectively describe naturalistic and lab animal behaviour also apply to human decision makers. Therefore, I developed a novel task to quantify the effect of key variables on the patch leaving decision, including costs to move between patches (delay and effort) and both foreground (patch) and background (environment) reward rates. In

this chapter I tested whether these factors had significant effects when manipulated in isolation (**EXPERIMENTS 1, 2 & 3**), and then in the more complicated combined setting (**EXPERIMENT 4**).

The results showed that as delay to reach the next patch increased, participants remained in each patch for longer. Furthermore, the degree of this behavioural shift (in seconds) was close to the predicted optimal change based on the MVT (**Figure 5-3**). Similarly, high (but not low) effort costs to move on also resulted in increased patch residency times, and I was able to quantify the impact of this behavioural change (in units of reward) using optimal foraging theory (**Figure 5-5**). Participants adjusted their behaviour to changes in background reward rate to a degree very close to MVT optimal predictions, and also demonstrated clear sensitivity to changes in the foreground (patch) reward rate (**Figure 5-7**). These effects remained significant when tested for in a combined version of the experiment (**Figure 5-9**). Furthermore, the presence of higher levels of apathy traits (in this young healthy group) was associated with greater sensitivity to changes in background reward rates – that is, people who were more apathetic demonstrated a greater behavioural change as background environment varied compared to those who were less apathetic. This finding was not present for foreground reward rate effects, nor delay or effort costs (**Figure 5-10**).

In addition to the specific behavioural changes associated with variations in each factor, participants also exhibited a bias to remain in patches for longer than was optimal based on the MVT calculations, an observation that has previously been made in many animal foraging studies. In sum, I found that human decision makers made foreground / background patch leaving decisions according to the predictions of the MVT, and that the presence of apathetic traits was associated with alterations in the effect of background reward rate – but not other factors – on patch leaving behaviour.

7.1.5 Chapter SIX

Two main questions were considered in this chapter. First, the hypothesis that changes in tonic dopamine levels would alter the effect of background reward environment on patch leaving behaviour was assessed. Additionally I hypothesised that apathy (in a PD

cohort) would also be characterised by an inability to utilise background reward information to guide foraging decisions. Therefore, over two experiments using the same patch leaving paradigm (**Figure 6-1**), I sought to establish a more nuanced view of the reward insensitivity associated with apathy in CADASIL and PD (**Chapters 2 and 4**) as well as the interplay between apathy, reward and the dopaminergic system.

In the first experiment I found that, consistent with my hypothesis, modulation of dopamine levels with the dopamine receptor agonist Cabergoline altered the influence of background – but not foreground – reward information on patch leaving behaviour (**Figure 6-3**). In the second experiment, in which 35 apathetic and non-apathetic PD patients completed the same paradigm ON and OFF their normal dopamine medications, I found a similar effect of changing dopamine levels on the use of background environment information, but only in patients with clinical apathy. That is, apathetic PD patients showed significant differences in the effect of background environment on patch leaving behaviour between ON and OFF states, whereas non-apathetic PD patients did not (**Figure 6-4**).

As with baseline dopamine levels, there was no influence of apathy on the effect of foreground (patch) reward rates, and nor were dopamine or apathy associated with a general change in patch leaving behaviour. Rather, their effects were specific to background environmental reward information. The results link tonic dopamine to background reward context. They suggest a mechanism (distinct from that explored in **Chapter 4**) by which disrupted dopaminergic pathways could result in apathy. More broadly they demonstrate the utility of more naturalistic decision making frameworks, such as provided by optimal foraging theory, for understanding complex behaviour syndromes such as apathy.

7.2 The underlying cognitive mechanisms of apathy

The philosopher and physician John Locke ascribed a crucial role for rewards (or *pleasure and pain*) in motivating actions, writing in *An Essay Concerning Human Understanding* that without these perceptions

"…we should have no reason to prefer one thought or action to another; negligence to attention, or motion to rest. And so we should neither stir our bodies, nor employ our minds, but let our thoughts (if I may so call it) run adrift, without any direction or design, and suffer the ideas of our minds, like unregarded shadows, to make their appearances there, as it happened, without attending to them. In which state man, however furnished with the faculties of understanding and will, would be a very idle, inactive creature, and pass his time only in a lazy lethargic dream."
(Locke, 1689)

Locke's description resonates with many elements of the findings presented in this thesis. These findings provide mechanistic evidence that apathy is associated with disrupted reward processing and a consequent reduction in motivated actions. But they also raise important issues and leave some questions unanswered – points that I address in the next section.

7.2.1 Are effort and reward truly dissociable constructs?

The experiments described in this thesis demonstrate that, just as Locke speculated, disruption of reward processing and concomitant decisions about actions underlies the syndrome of clinical apathy. Apathetic behaviour was characterised by diminished responsiveness to the rewarding outcomes of potential actions, as well as impaired ability to use information about background reward context to guide decisions (dependent on dopamine). These findings are novel and demonstrate a clear cognitive mechanism for the development of apathy. But is pursuing the hypothesis of disrupted *effort-based decision making* in fact somewhat tangential, and should the focus of research attention in fact be solely on reward systems? After all, apathetic patients were prepared to exert as much effort as non-apathetic patients, if rewards were high enough. Is effort actually relevant to understanding apathetic behaviour?

I would argue that, in keeping with the title of this thesis, effort – or more specifically the actions which effort represents – remain crucial to understanding the mechanisms underlying apathy and motivated behaviour more generally. Fundamentally actions and the outcomes that follow them are intrinsically linked. The brain processes and

integrates afferent sensory inputs to build, under the influence of memory systems, a model of the world. Why? To guide behaviour (Dennett, 2017). That is, actions or sequences of actions that lead to rewarding outcomes or avoid harmful outcomes (Salamone and Correa, 2012). Over evolutionary time the nature of rewards and actions have changed: most human behaviour does not involve simply moving towards a chemical gradient signalling a better nutritional harvest, but rather occurs within a complex, socially influenced backdrop. I would argue that whilst we perceive this environment with greater richness than our distant evolutionary ancestors, and have enhanced abilities to guide behaviour based on internal states – that is goal-directed behaviours – this underlying principle remains (Cohen et al., 2016; Mark et al., 2010).

Fundamentally, when we act, we do so to increase the likelihood of rewarding outcomes, whether that is being payed money, making a friend, eating a sandwich etc., or conversely to reduce the likelihood of an aversive outcome. And these actions have associated costs – energetic costs which we conceptualise as effort, and opportunity costs (the actions you can't make whilst undertaking your chosen one). So to act – to move, to be motivated – towards a rewarding outcome incurs a cost, a cost which is justified by the rewards it leads to. To consider rewards in isolation, in the absence of the behaviours that lead to them, is to miss their underlying neural significance – to motivate actions towards them. Therefore to say that apathy is associated with disrupted reward processing is, while true, also only telling half the story, because it is the consequences of this change on actions, and the weighing of action costs and outcomes, which leads to the reduction in goal directed behaviour that defines it.

7.2.2 Untested components of effort-based decision making in apathy

Apathy is associated with disrupted effort-based decision making. Specifically, apathetic patients are less willing to engage in actions for rewards, and show changes in their ability to utilise information about background reward context to guide switching behaviour, although the vigour of their motor responses seemed to be unaffected. But there are other components of effort-based decision making which have not been probed and could be relevant to the apathetic syndrome, particularly *persistence* and *learning*.

Persistence

Persisting with an action-set towards a temporally or spatially remote reward is considered one of the crucial properties of appetitive (instrumental) behaviour (Salamone and Correa, 2012). Furthermore, like other components of appetitive behaviour such as the vigour of response, persistence is strongly influenced by the mesolimbic dopaminergic system, particularly its projections into ventral striatum (Hamid et al., 2016; Howe et al., 2013; Salamone and Correa, 2012). The concept of persistence applies to a single behaviour towards a goal, but crucially also to the extended sequences of behaviours required to attain most rewarding outcomes relevant to humans (Holroyd and Yeung, 2012). In other words, persistence describes the cognitive process that maintains a behaviour from the decision to act to the consequences of that action. The ACC in particular has been implicated in maintaining these behaviours over extended time periods (Holroyd and McClure, 2015; Holroyd and Yeung, 2012; Silvetti et al., 2014; Verguts et al., 2015). Given the clear association between ACC disruption and apathy, failure of persistence towards a goal is another possible component that could contribute to the apathetic phenotype.

However, it is not enough to blindly persist towards an earlier selected goal – adaptive behaviour requires online monitoring of the chosen option against other possibilities – a process captured by foreground/background decision making and foraging models of behaviour. Intriguingly, neurophysiological and neuroimaging studies have shown that activity in the ACC tracks information about the value of a *current* plan, relative to alternatives, during extended sequences of actions that require persistence and effort in order to obtain desired outcomes (Blanchard et al., 2015; Croxson et al., 2009; Kolling et al., 2016; McGuire and Kable, 2015; Wittmann et al., 2016). Signals in the VS are also present during extended sequences of behaviour. Tonic dopaminergic signals within VS which modulate persistence towards a goal also convey information about background reward rate – a key determinant of the relative value of a current course of action, and the vigour with which it should be pursued (Hamid et al., 2016; Niv et al., 2007).

Future mechanistic investigations of apathy could therefore profitably focus on whether apathetic patients show a deficit in persisting with behaviours *once they have engaged with them*, particularly examining the interaction between persistence and tracking of

background reward context, given the findings in Chapter 6. It would be particularly interesting to probe whether, in a foreground / background decision making paradigm where patients executed a series of actions towards a goal, changing the background environmental option set would affect baseline levels of persistence (as it should), or whether apathetic patients would show a deficit in integrating such information to inform decisions about their current action set.

Learning

A final cognitive process to consider in relation to effort-based decision making and apathy is learning about the costs and consequences of actions (Le Heron et al., 2017). Most theoretical accounts of ACC and VS function suggest that, in addition to encoding information about the expected value of a course of action, these regions also represent any discrepancy between this prediction and the actual value once the behaviour is completed, under the principles of reinforcement learning theory (Kolling et al., 2016; Schultz and Dickinson, 2000). This discrepancy, or prediction error (PE), can be used to update estimates of the future value of acting.

A wealth of neurophysiological and neuroimaging evidence has demonstrated that ACC and VS activity signals PEs (Hauser et al., 2017; Hayden et al., 2011; Holroyd and Coles, 2008; Jocham et al., 2009; Lockwood et al., 2016; Matsumoto et al., 2007; O'Doherty et al., 2003; Rushworth and Behrens, 2008). The types of PE encoded in ACC and VS may be at least partly dissociable, with evidence suggesting that VS may be particularly important for stimulus-outcome associations, whilst ACC encodes PEs relating to the value of actions (Camille et al., n.d.; Hauser et al., 2017; Matsumoto et al., 2007; Scholl et al., 2015). Thus, there is abundant evidence that ACC and VS encode information about the outcomes of our actions, information which can then drive learning about which behaviours are worth performing in the future.

How could this be relevant to apathy? Apathetic behaviour in some individuals could arise if learning is systematically biased by alterations in these neural regions. An increased weighting between a course of action and its effort costs could result in an overestimation, or hypersensitivity to these costs during subsequent decisions. A down-weighting of learning about how actions relate to rewarding outcomes could lead to reward insensitivity. Any change in the balance between these two learning processes

could alter the weighing up of costs and rewards as an individual decides if an action *is worth it.*

Notably, one study has examined such outcome-related activity in apathetic and non-apathetic PD patients. Patients with apathy had a blunted feedback related negativity signal (measured by EEG) during a gambling task, a signal which is thought to originate in the ACC and drive learning (Martinez-Horta et al., 2014b). These changes could conceivably result, over time, in the pattern of decision making behaviour observed in apathetic PD patients in chapter 4, in which a higher threshold of reward was required to trigger acceptance of effortful offers. Future work should explore this area further, particularly examining effort-related (as well as reward-related) outcome signals (Hauser et al., 2017). A difficulty with such studies will be that these putative changes may in fact pre-date the development of apathy (as a potential initiating factor). An ideal study would therefore be conducted longitudinally, aiming to predict those who would develop apathy according to their baseline behavioural and physiological learning metrics. This would however be resource intensive and require persistence over an extended period of time on the part of the investigators.

Vigour

Finally, it is worth noting that another component of effort-based decision making – the vigour of response towards a goal – was not changed in apathy whether assessed by peak motor squeeze (CADASIL and PD) or saccadic eye movement velocity (CADASIL). Both of these motor responses were externally cued – by a peripheral target location for saccadic eye movements and a bar on a cartoon tree for force exertion. However vigour selection can itself be viewed as a decision (Le Bouc et al., 2016; Zenon et al., 2016) and indeed varies with dopamine state (Chapter 4). Additionally vigour is seen as a key component of instrumental behaviour, and has been linked, via the dopaminergic system, to background reward rate (Hamid et al., 2016; Niv et al., 2007; Salamone and Correa, 2012). It is therefore somewhat surprising that apathetic patients displayed normal vigour of responses.

This might be explained by an insufficiently sensitive measurement of vigour. For example, although there was a main effect of reward on saccadic velocity, this appeared less robust within the apathy group, although notably there was no significant

apathy*reward interaction. A task specifically designed to examine vigour, and in particular vigour of self-generated (rather than externally cued) actions, would be an important future step before concluding that the vigour of responses is indeed unaffected in apathy. Such a task could potentially also examine persistence over an extended period of time and the effect of varying background reward. These components should be directly related to vigour (Niv et al., 2007) and were associated with apathy in Chapter 6.

7.2.3 A cognitive fingerprint of disrupted effort-based decision making in apathy

Aside from investigating how these other aspects of effort-based decision making relate to apathy, a crucial next step is to understand how alterations in these different components map onto different patients. Are changes in some components specific to certain diseases? Or are there discernible neural differences that relate different components of effort-based decision making to different groups of apathetic individuals transdiagnostically? Answering questions such as these is crucial to understanding how the alterations identified in individual experiments relate together as a whole, and could have significant implications in terms of tailoring therapeutic strategies. The idea of cognitive fingerprints as a way of conceptualising such information has been proposed in relation to other system-level disorders like neurodegenerative diseases (Rossor et al., 2010). A similar construct could be applied to the different components of effort-based decision making, assessed using behavioural and physiological measures (**Figure 7-1**). This approach would require a combined assessment of each apathetic patient, but would form an important base from which to explore these clinically relevant questions and, in the future, guide treatment strategies.

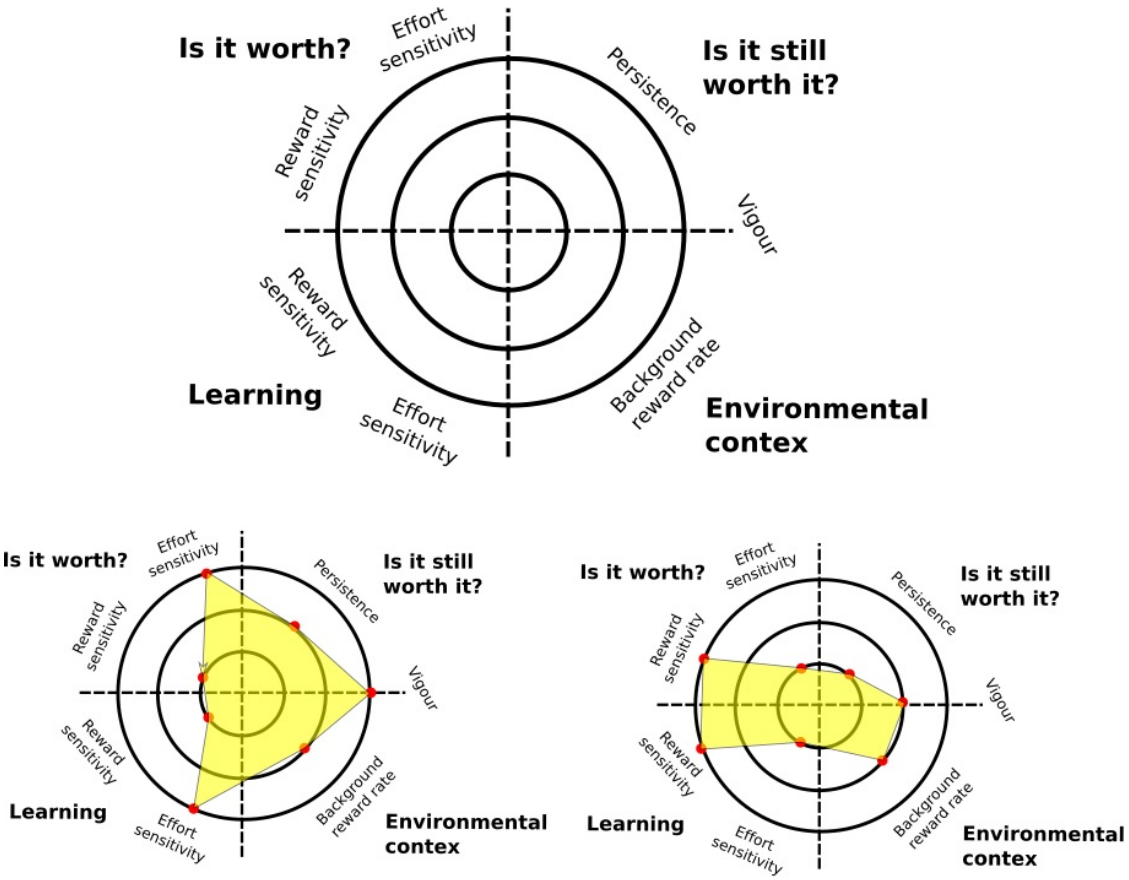


Figure 7-1. A hypothetical cognitive fingerprint for disrupted effort-based decision making in apathy

Apathetic patient performance on different components of effort-based decision making could be assessed using behavioural and physiological metrics and compared to controls. Specific patterns of apathy may be discernible, e.g. predominantly affecting reward processing in engagement decisions and learning (**bottom left**), or hypersensitivity to effort costs and reduced vigour and persistence (**bottom right**).

7.2.4 Apathy and neuromodulatory systems – dopamine and beyond

There is a clear scientific basis for considering the mesolimbic dopaminergic system as a primary influence over, and potential therapeutic target for apathy (Adam et al., 2013; Hamid et al., 2016; Kurniawan et al., 2011; Salamone and Correa, 2012; Santangelo et al., 2015). However, the work in this thesis illuminates a more nuanced understanding of this relationship, associating apathy and dopamine in some, but not all components of effort-based decision making. These findings may in part explain the failure of some clinical trials of dopamine agonists to treat apathy (Chung et al., 2016).

But if not dopamine then what else? Recent basic neuroscience work has also begun to emphasise the importance of non-dopaminergic systems in aspects of effort-based decision making (Bailey et al., 2016a). Particular interest has been paid to the serotonergic 5-HT_{2C} receptor, which is expressed in neural regions including VTA, VS and ACC and is considered to play a crucial role in modulating goal-directed behaviour (Bailey et al., 2016b; Higgins and Fletcher, 2003). Furthermore preliminary clinical data has demonstrated Agomelatine, a 5-HT_{2C} receptor inverse agonist (which stimulates the receptor to *reduce* activity), can effectively treat apathy in patients with frontotemporal dementia (Callegari et al., 2016).

The cholinergic neuromodulatory system and adenosine 2_A receptors have also attracted interest. Stimulation of these receptors has a similar effect on effort-based decision making as dopamine antagonism, whilst adenosine antagonists can 'rescue' goal directed behaviour following administration of dopamine antagonists (Nunes et al., 2010). Similarly the direct stimulation of muscarinic cholinergic receptors within ventral striatum (but not other striatal regions) also reduces goal-directed activity in a similar pattern to dopaminergic antagonism (Nunes et al., 2013).

Interestingly the effects of these other neuromodulators are still tied to the mesolimbic dopaminergic system. Stimulation of the 5-HT_{2C} receptor reduces DA neuron firing rates within VTA and substantia nigra (Alex and Pehek, 2007). Adenosine 2A receptors co-localise with D2 receptors on striatal medium spiny neurons (Nunes et al., 2010), whilst cholinergic receptors are similarly associated with both D1 and D2 receptors in this region (Nunes et al., 2013). This illustrates the complexity inherent in understanding the role of neuromodulatory systems in goal-directed behaviour, with effects of one system dependent on the activity within others. Furthermore, given that many neurodegenerative disorders are characterised by loss of multiple neuromodulatory pathways, attempting to correct just one deficit without attending to others may significantly reduce the likelihood of clinical efficacy. As our understanding of the basic interactions between these systems grows, the opportunity to tailor pharmacological therapies more closely to a desired therapeutic effect may arise.

7.2.5 Treatment implications

The take home therapeutic message from chapters 2, 3 and 4 is that apathetic patients are still prepared to exert effort for rewards, but the incentivisation associated with the reward needs to be higher – particularly for the relatively low reward outcomes that constitute much of our daily activities. This suggests manipulations that increase the perceived value of a given reward are likely to increase actions towards these outcomes. Although dopaminergic stimulation increased effortful behaviour for reward, this occurred along a separate axis to the apathetic deficit, affecting mainly high reward/high effort options. VS dopamine may signal the value of work when weighing up potential actions (Hamid et al., 2016), but may be less important for activating low effort, lower reward actions (Salamone et al., 2007). Drugs, such as Agomelatine, that target other neuromodulatory systems show promise (Callegari et al., 2016), however further information about their mechanism of action as it relates to apathy is needed. It is probably too early to realistically contemplate combined therapies (as discussed in the previous paragraph) but with increasing understanding this may be an option.

Another potential strategy would be to focus on the energisation of behaviour – in effect by-passing the reward/effort trade-off. The noradrenergic system has been ascribed a crucial role in overcoming the *difficulty* (as opposed to costs) of effortful behaviour – that is, mobilising resources to energise effortful behaviour (Gorman and Sullivan, 2000; Varazzani et al., 2015). Future work might profitably examine whether its upregulation increases goal-directed behaviour, even in the absence of a specific effect on reward valuation.

In contrast to the first series of experiments, in the work presented in Chapter 6 dopamine exerted a *direct* effect on apathetic behaviour, improving apathetic PD patients' use of background reward information to guide patch leaving decisions. The use of foraging models to explore apathy mechanisms is still in its infancy. However, if this proves to be a useful construct to explain apathetic behaviour more generally, the results suggest that apathetic patients are particularly vulnerable to dopaminergic reductions, and may benefit from measures to increase, or maintain, tonic dopamine levels.

Finally, it is worth considering non-pharmacological manipulations. The results in Chapter 2 and 4 suggest that, once apathetic patients had decided to exert effort for reward, they did so in the same manner as non-apathetic patients. Similarly externally-cued actions (saccadic velocity) in Chapter 3 were normal in apathetic patients despite their reward insensitivity. These findings suggest that, simply, if apathetic patients are cued to undertake activities they can execute them normally. Cueing can take different forms, including an attentive spouse, smartphone reminders, alarms etc. Probably most important is to educate the family and carers of apathetic patients about the importance of prompting activities on a day to day basis.

7.2.6 Towards a deeper understanding of effort-based decision making

There is growing evidence that signals in both ACC and VS are modulated by the value of a chosen action *during* sequences of actions, as well as crucially the value of alternatives and other properties of the environment. This evidence has been part of a shift in the conceptualisation of effort-based decision making, from standard economic models of binary choice, to a more ecologically derived opportunity cost framework of decision making – a framework which is well described by foraging theories of behaviour and may be directly relevant to how we view the apathetic syndrome (Pearson et al., 2014).

The experiments in chapter 5 and 6 demonstrate the utility of a foreground-background decision making framework for describing normal human behaviour and investigating behavioural disorders such as apathy. However, much is still to be understood about the neural mechanisms by which this process may occur. I have presented evidence that tonic dopamine plays an important role in signalling information about background reward rate to guide decisions, but it remains unclear how such a signal is integrated with foreground information to guide choice. Neuronal recordings from macaque ACC suggest an accumulate-to-bound mechanism may apply, whereby neural activity increases to a threshold which corresponds to selection of a particular behaviour (‘moving on’ in the patch-leaving context) (Hayden et al., 2011). A similar ramping signal mechanism is thought to underlie perceptual decisions (Gold and Shadlen, 2007).

There are two key questions which could be addressed using the behavioural paradigm developed in Chapter 5. Firstly, can a ramping neural signal corresponding to behavioural switches be demonstrated in human decision makers? The paradigm is designed to capture decisions that evolve over temporally extended periods, meaning ramping neural activity may be amenable to capture by either fMRI or EEG. Another potential source is by recording local field potentials using deep brain stimulation electrodes which are sometimes implanted within ACC for treatment of chronic pain (Russo and Sheth, 2015). If such a signal could be demonstrated, an obvious next step would be to explore how changes in tonic dopamine levels (e.g. via drug administration as in the first experiment of chapter 6) influence this signal. Would an increase in tonic dopamine lower the threshold for switching behaviour? Or change the gain of signal accumulation? And similarly, how do effort costs (e.g. to move on, as in the behavioural paradigm) impact this signal?

Secondly – and related to these latter points – is apathy associated with an increased threshold to activating behaviour? Or reduced gain of signal? Or potentially a shift in the starting point of the signal? Very preliminary evidence in favour of such a mechanism is demonstrated by the increased decision time associated with apathy in CADASIL patients, as well as the lack of discrepancy in times to accept or reject decisions (in comparison to non-apathetic CADASIL patients and HCs who accepted offers quicker than they rejected them).

These investigations would allow a deeper mechanistic understanding of apathy and decision making, but will rely on effective paradigms to probe questions of interest, and techniques that can detect relevant neural signals.

7.2.7 Beyond decisions – other potential contributors to amotivated behaviour

The discussion thus far has been limited to components of effort-based decision making. Simply, I have emphasised three phases of behaviour that may be relevant to apathy:

- Choosing whether to perform an action/series of actions – *is it worth it?*

- Sustaining the behaviour with reference to the background reward context – *persistence and is it still worth it?*
- Learning through outcome monitoring – *was it worth it?*

However, there are other cognitive processes relevant to normal goal-directed behaviour. It is also notable that changes in effort-based decision making and reward sensitivity have tended to correlate with only particular sub-scales of the LARS – namely the action initiation scale. This subscale emphasizes a person's daily activities and ability to initiate these activities, however the lack of correlation between task metrics and other subscales (such as those labelled intellectual curiosity and emotion) suggests there are other facets of what we currently conceptualise as apathy that are not explained by deficits in effort-based decision making alone.

Other phases of motivated behaviour to consider include:

- Identifying potential goals – *what could I do?*
- Enacting sequences of behaviours towards a goal – *how to do it?*

Option Generation

The process of generating potential options for behaviour provides crucial inputs for subsequent decision making and has been linked to function within anterolateral prefrontal cortex (Kaiser et al., 2013). The design fluency task reported in Chapter 2 (**Appendix 2**), in which participants had to generate as many novel designs as possible by joining dots with lines within a two minute provided a coarse metric of this process, and was not significantly different between apathetic and non-apathetic patients. However further work could usefully investigate this concept.

Enacting behaviour towards goals

The *ability to coordinate thoughts and actions in relation with internal goals* is a multi-faceted construct often subsumed within the term *cognitive control* (Koechlin et al., 2003). Key components include working memory, cognitive flexibility, inhibition and planning, and these components are often referred to collectively as executive functions (Diamond, 2013). These component processes are thought to be instantiated within prefrontal cortex (Koechlin et al., 2003). Some models suggest these processes occur within a hierarchical framework controlled by the ACC (which sets goals and provides ongoing 'motivation' to achieve them – Botvinick, 2012). Previous conceptualisations of apathy include a specific 'cognitive inertia' component referring to dysfunction of the above processes, associated with DLPFC-dorsal striatum loop damage (Levy and Dubois, 2006; Pagonabarraga et al., 2015).

Although less consistent than ACC and VS, dysfunction in dorsolateral prefrontal cortex (DLPFC) has been associated with apathy by some authors (Bruen et al., 2008; Thobois et al., 2010; Zamboni et al., 2008). Furthermore disruption of one of these cognitive processes – planning (as assessed by Tower of London-Drexel test) – was associated with apathy in a cohort of PD patients (Weintraub et al., 2005). Interestingly however, in the current studies neither apathy in CADASIL nor PD was associated with significantly reduced performance on neuropsychological tasks assessing executive functions (digit span, trail making task, design fluency task). These tasks may however lack the fine-grained assessment necessary to detect more subtle changes, and future work using specialised tasks (e.g. Fallon et al., 2017) would be important to further explore the association between executive dysfunction and apathy.

Finally, a separate "auto-activation deficit" component has also been proposed to cause apathy in some patients, associated in particular with subcortical damage to GPi (Levy and Dubois, 2006; Pagonabarraga et al., 2015). It is viewed as a severe form of apathy, in which patients do and say very little, and tend to describe their minds as "empty" (Levy and Dubois, 2006). Mechanistically, it has been proposed to occur because potential voluntary behaviours do not reach an activation threshold, either because of reduced signal-to-noise within the basal ganglia-prefrontal cortex feedback system (because of impaired amplification of relevant signals), or more simply because of reduced outflow signal to PFC from the damaged GPi (Levy and Dubois, 2006). Such a

deficit could, at least in part overlap with components of effort-based decision making such as evaluating whether an action is *worth it*, particularly if such decisions depend on accumulation of evidence (in the form of neural signal) towards a bound (Gold and Shadlen, 2007). However this, as with the role of executive functions in goal directed behaviour, requires further mechanistic study.

7.2.8 Systems of behaviour underlying apathy – a role for bad habits?

That apathy is a disorder of goal directed behaviour is essentially sine qua non (Levy and Dubois, 2006; Robert et al., 2009). This thesis has focussed on mechanisms central to such a system of behaviour. However, there is no empirical evidence to suggest other systems of behaviour are preserved in apathy, in particular habitual behaviour. Habitual behaviour is based on stimulus-response representations, with actions that lead to better than expected outcomes reinforced according to the principals of reinforcement learning, making them more likely to occur when the same stimulus is again encountered (Balleine and O'Doherty, 2010). This process is particularly dependent on dorsal striatum and the dopaminergic neuromodulatory system (Daw and O'Doherty, 2014). Behavioural disturbances such as impulsivity, which interestingly often co-occurs with apathy (Lansdall et al., 2017; Sinha et al., 2013) are associated with disruption of these cortical-subcortical loops (Dalley et al., 2011).

Many of the behaviours that apathetic patients don't do, such as cleaning the house or making a cup of tea, are probably normally performed under the guidance of habitual systems. Furthermore, dysfunction within the habitual system would mean all instrumental behaviours would need to be instigated via the more cognitively demanding goal directed system – which itself is clearly affected in apathy. Future research might investigate the formation and maintenance of habitual behaviour in apathetic patients. Impairment of this system would have implications for both non-pharmacological (e.g. over-training patients on basic activities) and pharmacological treatments (e.g. manipulating the dopaminergic system).

7.2.9 Apathy – a devolving concept?

The focus in the thesis has been to start from underlying neurobiological systems and work upwards, understanding the components of apathy in terms of dysfunction of underlying normal mechanisms. This approach has been promoted recently by the National Institute of Mental Health in the Research Domain Criteria framework for understanding psychiatric conditions (Holroyd and Umemoto, 2016; NIMH, n.d.). However, it remains unclear how such an approach should fit with existing apathy conceptualisations – particularly those based on questionnaires which identify separate components of apathy. For example, the 'emotional' scale within the LARS contains questions focussed on a person's emotional reactivity to events around them, but is not clearly linked to a specific neurobiological process. It could relate to a separate neurobiological mechanism from effort-based decision making, for example hedonic systems (Berridge and Kringelbach, 2015)? If so, is it useful to consider these changes within the same syndrome as disrupted effort-based decision making?

To some degree the co-occurrence of these symptoms (which led to them being classified as part of the same apathetic syndrome in the first place) highlights the reason for continuing to view apathy in such a way. However as mechanistic understanding grows, and particularly as treatments arise which are tailored to disrupted underlying mechanisms, dispensing with syndromic labels in favour of more specific, biologically relevant classifications is likely to be advantageous – in much the same way as considering anhedonia and dysphoria as separate constructs within major depressive disorder (Treadway and Zald, 2011), or distinguishing neuro-myelitis optica from multiple sclerosis (Wingerchuk et al., 2006) – has led to different clinical profiles and treatment strategies.

Moving ahead, the field must decide whether reduced goal directed behaviours resulting from, for example, disrupted executive functions truly constitutes a *disorder of motivation* that should be described as apathy. We would not describe a person who is motivated to climb a mountain, but unable to do so because of bilateral above knee amputations, as apathetic. So should somebody who is motivated to fix their car, but unable to plan the necessary steps nor attend to the problem for long enough fall under

this category? A similar analogy can be made between an auto-activation deficit and a patient who is unconscious due to disruption of their reticular activating system. The answer likely lies in the grey areas between these extreme examples, and will depend on continued improvements in neurobiological understanding of normal motivated behaviour.

7.2.10 Concluding remarks

In this thesis I have outlined and demonstrated evidence for considering apathy as a disorder of effort-based decision making and its constituent components. This normal cognitive process lies at the heart of motivated, goal-directed behaviour. Linking its disruption to apathy provides a mechanistic explanation for the reduced goal directed behaviour that currently defines the apathetic syndrome, across underlying pathologies. It remains unclear the extent that other processes may also contribute to apathy. As understanding of normal cognitive functions improve, it is likely that terms such as apathy will become less important, as behavioural changes are understood and treated based on their component processes. For now, we remain in transition – reconciling the syndromic descriptions of the past, which have captured the clinical essence of apathy, with the neurobiological models of the present. As we look to the future, it is this integration which promises to illuminate the mechanisms of complex behavioural syndromes such as apathy.

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Appendix 1 – Questionnaire measures

Lille Apathy Rating Scale

Everyday productivity
What do you do during the day? Tell me about your day-to-day life
Time taken to reply:
Number and variety of activities mentioned:

Interests
What are you interested in? What do you like doing to keep yourself occupied?
Time taken to reply:
Number of activities mentioned:
How often do you… ?

Taking the initiative
In general, do you decide to do things or does someone have to push you a little?
When you have to go to an appointment, a meeting or a formal occasion, do you have to be told to get yourself ready?
When you have to make an appointment (for example with the doctor or dentist), do you do it yourself or do you wait for someone to do it for you?
Do you take part spontaneously in daily living activities or do you need to be asked?

Novelty seeking
Do you like finding out about something new (a new TV programme or a new book)?
Do you like trying out new products, tools or recipes that you're not familiar with?
Do you like visiting places you've never been to before?
When you go out for a drive or when you're travelling by train or bus, do you enjoy looking at the countryside, the houses?

Motivation – Voluntary actions
When you decide to do something, are you easily able to make an effort or is it difficult?
When you don't manage to do something, do you try to find other solutions?
When you decide to do something, do you see it through to the end or do you tend to give up?
When you can't find something (for example a document or an object), do you go to a lot of trouble looking for it?

Emotional responses
When you watch a film, do you easily become emotional or moved?

When someone tells you a joke or when you watch a comedy sketch on TV, do you laugh easily?
Do you feel happy when you hear some good news?
Do you feel sad when you hear some bad news?

Concern

When you have a problem (for example when your TV set breaks down), does it worry you?
When something's not working or when something unexpected happens, do you think about finding a solution?
When your partner or children have a minor problem (when they're ill, for example), does that concern you, do you worry about them?
Do you like to ask how your family and friends are on a regular basis?

Social life

Do you have friends?
When you meet friends, do you enjoy spending time with them or is it a chore?
In conversation, do you start talking or do the others tend to speak to you first?
During a discussion, do you give your own opinion spontaneously or do you fall into line with someone else's opinion?

Self-awareness

When you've finished doing something, do you take stock of the situation and think about what is going well and what's not?
After having taken a decision, do you sometimes think that you've made the wrong choice?
When you've been unpleasant to someone, do you sometimes feel guilty afterwards?
If, during a discussion, you realise that you're in the wrong, are you able to admit it – at least to yourself?

Sub-scales		Scores
Everyday productivity	EP	-4 -3 -2 -1 0 1 2 3 4
Interests	INT	-4 -3 -2 -1 0 1 2 3 4
Taking the initiative	INI	-4 -3 -2 -1 0 1 2 3 4
Novelty seeking	NS	-4 -3 -2 -1 0 1 2 3 4
Motivation - Voluntary actions	M	-4 -3 -2 -1 0 1 2 3 4
Emotional responses	ER	-4 -3 -2 -1 0 1 2 3 4
Concern	C	-4 -3 -2 -1 0 1 2 3 4
Social life	SL	-4 -3 -2 -1 0 1 2 3 4
Self-awareness	SA	-4 -3 -2 -1 0 1 2 3 4

Factorial sub-scores are calculated from sub-scale scores using the formulas given below.

Factorial sub-scores			Scores
Intellectual curiosity	(INT+NS+M+SL)/4	IC	-4 -3 -2 -1 0 1 2 3 4
Emotion	(ER+C)/2	E	-4 -3 -2 -1 0 1 2 3 4
Action initiation	(EP+INI)/2	AI	-4 -3 -2 -1 0 1 2 3 4
Self-awareness	(SA)	SA	-4 -3 -2 -1 0 1 2 3 4

Apathy Evaluation Scale

For each question, circle the answer that best describes your thoughts, feelings, and actions during the past 4 weeks.

	Not at all characteristic of me	***Slightly characteristic of me***	***Somewhat characteristic of me***	***Very characteristic of me***
1. I am interested in things.	*1*	*2*	*3*	*4*
2. I get things done during the day.	*1*	*2*	*3*	*4*
3. Getting things started on my own is important to me.	*1*	*2*	*3*	*4*
4. I am interested in having new experiences.	*1*	*2*	*3*	*4*
5. I am interested in learning new things.	*1*	*2*	*3*	*4*
6. I put little effort into anything.	*1*	*2*	*3*	*4*
7. I approach life with intensity.	*1*	*2*	*3*	*4*
8. Seeing a job through to the end is important to me.	*1*	*2*	*3*	*4*
9. I spend time doing things that interest me.	*1*	*2*	*3*	*4*
10. Someone has to tell me what to do each day.	*1*	*2*	*3*	*4*
11. I am less concerned about my problems than I should be.	*1*	*2*	*3*	*4*
12. I have friends.	*1*	*2*	*3*	*4*
13. Getting together with friends is important to me.	*1*	*2*	*3*	*4*
14. When something good happens, I get excited.	*1*	*2*	*3*	*4*
15. I have an accurate understanding of my problems.	*1*	*2*	*3*	*4*
16. Getting things done during the day is important to me.	*1*	*2*	*3*	*4*
17. I have initiative.	*1*	*2*	*3*	*4*
18. I have motivation.	*1*	*2*	*3*	*4*

Geriatric Depression Scale

Choose the best answer for how you have felt over the last week.

No	Question	Answer
1.	Are you basically satisfied with your life?	Yes/No
2.	Have you dropped many of your activities and interests?	Yes/No
3.	Do you feel that your life is empty?	Yes/No
4.	Do you often get bored?	Yes/No
5.	Are you in good spirits most of the time?	Yes/No
6.	Are you afraid that something bad is going to happen to you?	Yes/No
7.	Do you feel happy most of the time?	Yes/No
8.	Do you often feel helpless?	Yes/No
9.	Do you prefer to stay at home, rather than going out and doing new things?	Yes/No
10.	Do you feel you have more problems with memory than most people?	Yes/No
11.	Do you think it is wonderful to be alive?	Yes/No
12.	Do you feel pretty worthless the way you are now?	Yes/No
13.	Do you feel full of energy?	Yes/No
14.	Do you feel that your situation is hopeless?	Yes/No
15.	Do you think that most people are better off than you are?	Yes/No
		A /3
		D /12
		TOTAL

Beck's Depression Inventory – II

1. Sadness

0 I do not feel sad.
1 I feel sad much of the time.
2 I am sad all the time.
3 I am so sad or unhappy that I can't stand it.

2. Pessimism

0 I am not discouraged about my future.
1 I feel more discouraged about my future than I used to be.
2 I do not expect things to work out for me.
3 I feel my future is hopeless and will only get worse.

3. Past Failure

0 I do not feel like a failure.
1 I have failed more than I should have.
2 As I look back, I see a lot of failures.
3 I feel I am a total failure as a person.

4. Loss of Pleasure

0 I get as much pleasure as I ever did from the things I enjoy.
1 I don't enjoy things as much as I used to.
2 I get very little pleasure from the things I used to enjoy.
3 I can't get any pleasure from the things I used to enjoy.

5. Guilty Feelings

0 I don't feel particularly guilty.
1 I feel guilty over many things I have done or should have done.
2 I feel quite guilty most of the time.
3 I feel guilty all of the time.

6. Punishment Feelings

0 I don't feel I am being punished.
1 I feel I may be punished.
2 I expect to be punished.
3 I feel I am being punished.

7. Self-Dislike

0 I feel the same about myself as ever.
1 I have lost confidence in myself.
2 I am disappointed in myself.
3 I dislike myself.

8. Self-Criticalness

0 I don't criticize or blame myself more than usual.
1 I am more critical of myself than I used to be.
2 I criticize myself for all of my faults.
3 I blame myself for everything bad that happens.

9. Suicidal Thoughts or Wishes

0 I don't have any thoughts of killing myself.
1 I have thoughts of killing myself, but I would not carry them out.
2 I would like to kill myself.
3 I would kill myself if I had the chance.

10. Crying

0 I don't cry anymore than I used to.
1 I cry more than I used to.
2 I cry over every little thing.
3 I feel like crying, but I can't.

11. Agitation

0 I am no more restless or wound up than usual.

1 I feel more restless or wound up than usual.

2 I am so restless or agitated that it's hard to stay still.

3 I am so restless or agitated that I have to keep moving or doing something.

12. Loss of Interest

0 I have not lost interest in other people or activities.

1 I am less interested in other people or things than before.

2 I have lost most of my interest in other people or things.

3 It's hard to get interested in anything.

13. Indecisiveness

0 I make decisions about as well as ever.

1 I find it more difficult to make decisions than usual.

2 I have much greater difficulty in making decisions than I used to.

3 I have trouble making any decisions.

14. Worthlessness

0 I do not feel I am worthless.

1 I don't consider myself as worthwhile and useful as I used to.

2 I feel more worthless as compared to other people.

3 I feel utterly worthless.

15. Loss of Energy

0 I have as much energy as ever.

1 I have less energy than I used to have.

2 I don't have enough energy to do very much.

3 I don't have enough energy to do anything.

16. Changes in Sleeping Pattern

0 I have not experienced any change in my sleeping pattern.

1a I sleep somewhat more than usual.

1b I sleep somewhat less than usual.

2a I sleep a lot more than usual.

2b I sleep a lot less than usual.

3a I sleep most of the day.

3b I wake up 1–2 hours early and can't get back to sleep.

17. Irritability

0 I am no more irritable than usual.

1 I am more irritable than usual.

2 I am much more irritable than usual.

3 I am irritable all the time.

18. Changes in Appetite

0 I have not experienced any change in my appetite.

1a My appetite is somewhat less than usual.

1b My appetite is somewhat greater than usual.

2a My appetite is much less than before.

2b My appetite is much greater than usual.

3a I have no appetite at all.

3b I crave food all the time.

19. Concentration Difficulty

0 I can concentrate as well as ever.

1 I can't concentrate as well as usual.

2 It's hard to keep my mind on anything for very long.

3 I find I can't concentrate on anything.

20. Tiredness or Fatigue

0 I am no more tired or fatigued than usual.

1 I get more tired or fatigued more easily than usual.

2 I am too tired or fatigued to do a lot of the things I used to do.

3 I am too tired or fatigued to do most of the things I used to do.

21. Loss of Interest in Sex

0 I have not noticed any recent change in my interest in sex.

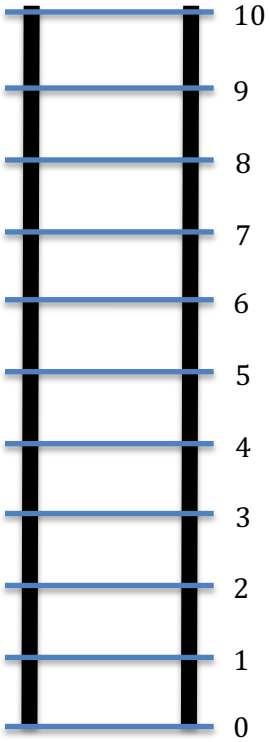
1 I am less interested in sex than I used to be.

2 I am much less interested in sex now.

3 I have lost interest in sex completely.

Cantril Ladder

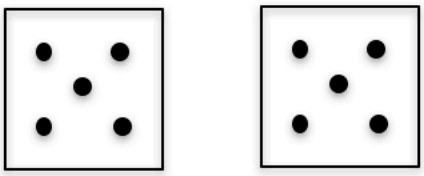
Please imagine a ladder with steps numbered from 0 at the bottom to 10 at the top. The top of the ladder represents the best possible life for you, and the bottom of the ladder represents the worst possible life for you. On which step of the ladder would you say you personally feel you stand at this time?



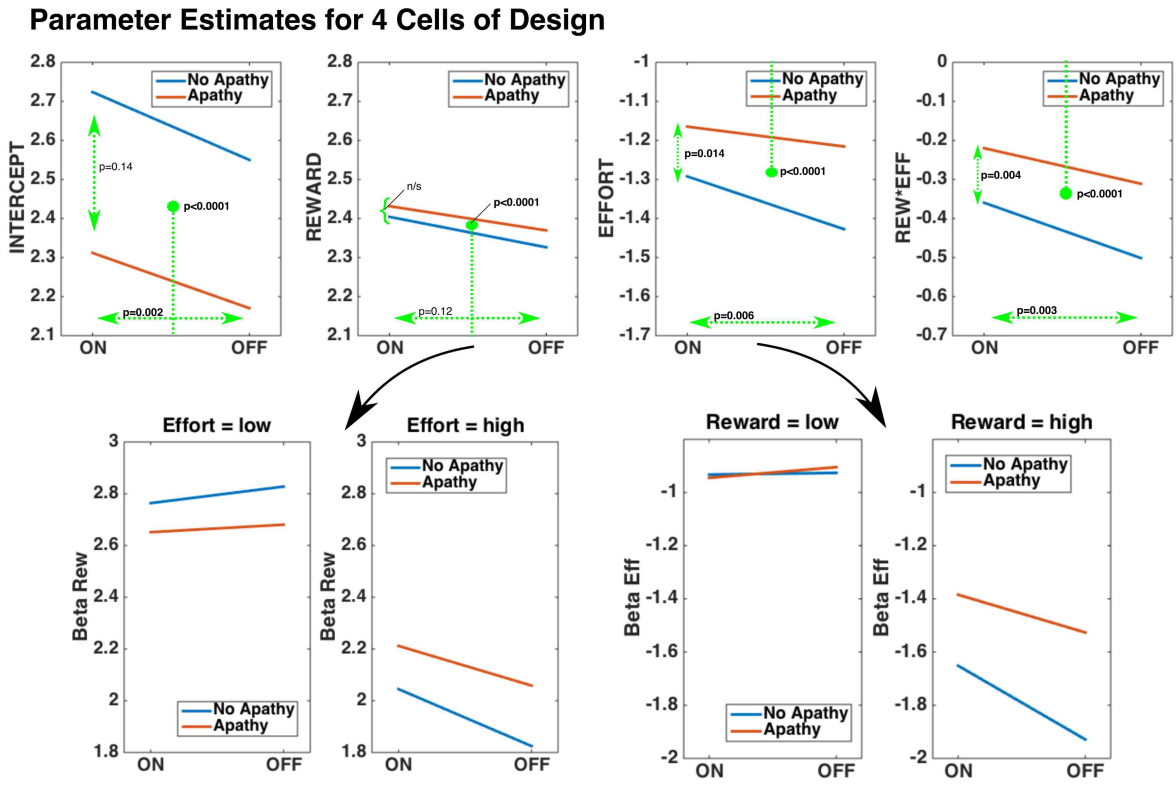
Appendix 2 – Design fluency task

There are a number of squares, each containing 5 dots, on the sheet of paper in front of you. I want you to draw as many designs as possible within the next 2 minutes by connecting 2 or more dots with straight lines. Not all dots per square have to be used. Please do not repeat any designs or draw lines that do not connect dots.

EXAMPLE



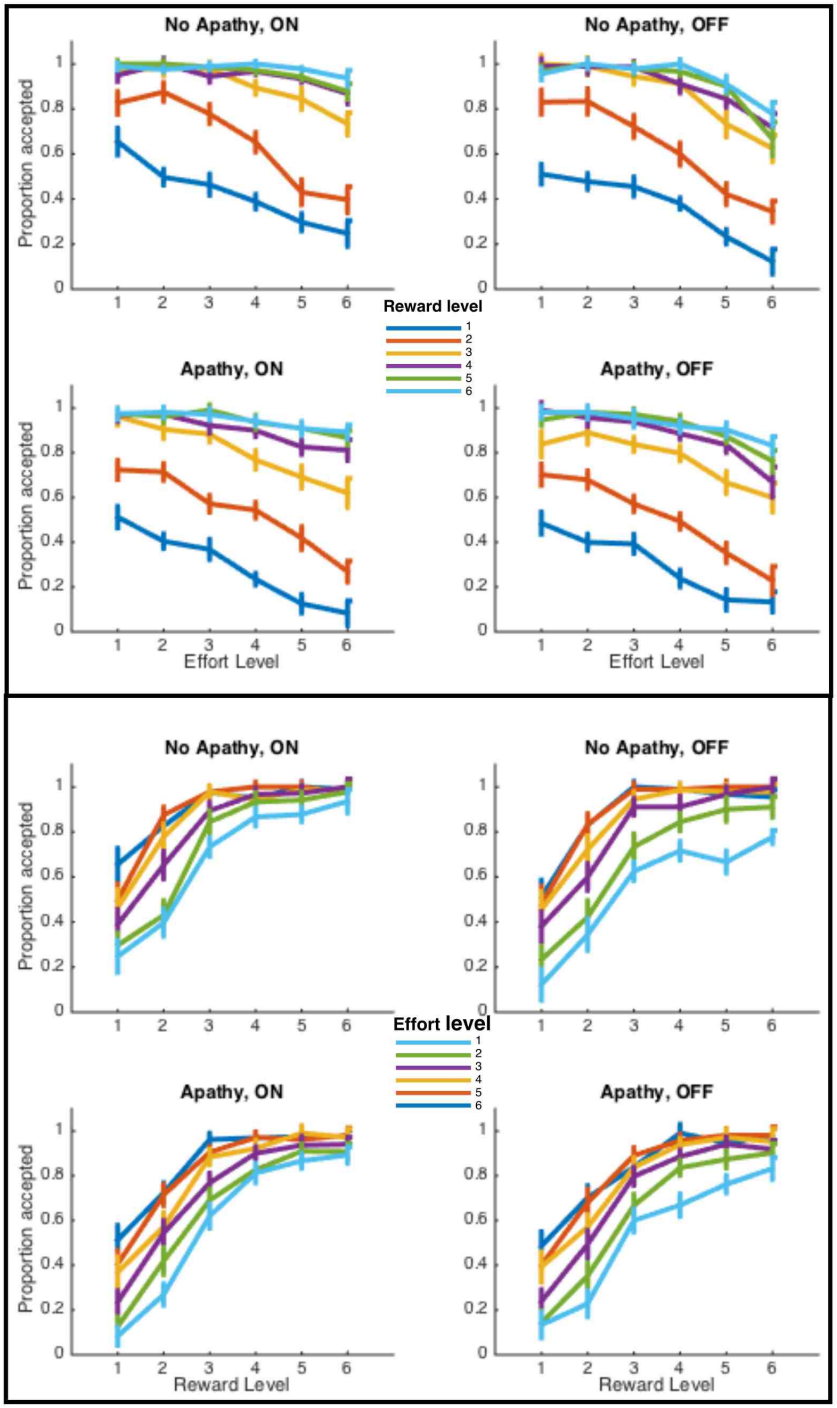
Appendix 3 – Chapter four additional analyses



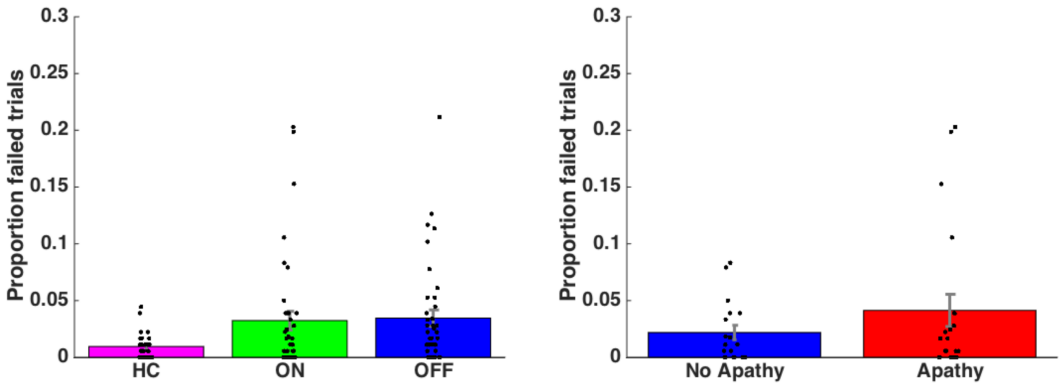
Appendix figure. Parameter estimates for the 4 groups of the design – No Apathy ON, Apathy ON, No Apathy OFF and Apathy OFF.

Top panels: Parameter estimates for Intercept, Reward, Effort and Reward*Effort, for the 4 cells of Design matrix; p values from full model are displayed.

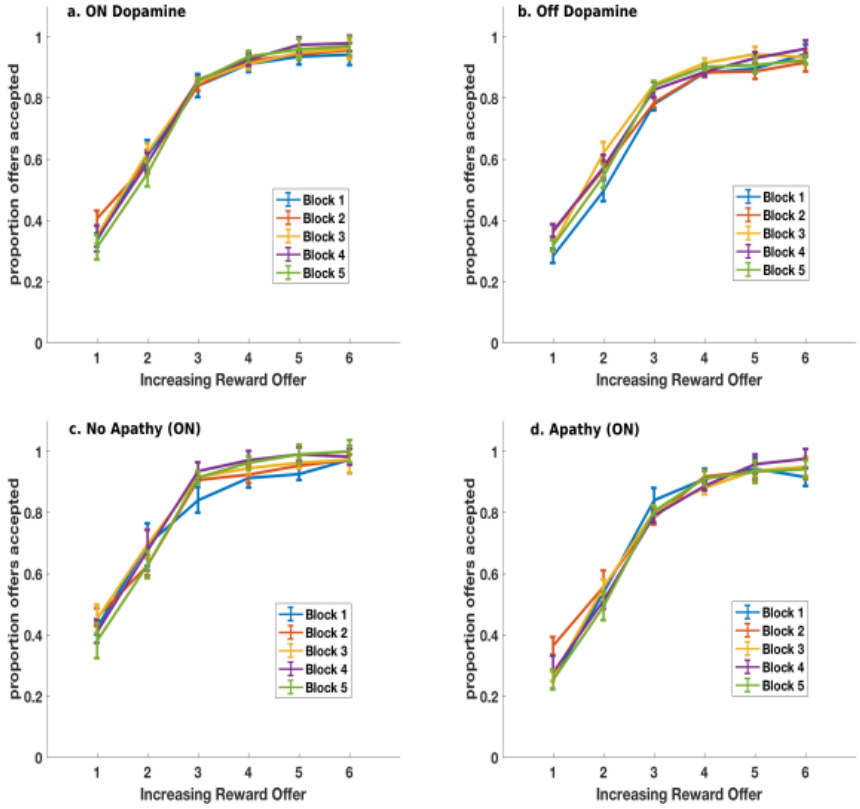
Bottom panels: The two significant 3-way interactions (**apathy*reward*effort** and **dopamine*reward*effort**) are illustrated, by showing how the parameter estimate for reward (left panels) and effort (right panels) varies for high and low effort and reward respectively. **For dopamine**, the *reward* regression slope becomes shallower in the OFF state, at HIGH *effort* levels, whilst *effort* becomes more costly in the OFF state at HIGH *reward* levels. This manifests as a *reduction in choice for High Effort, High Reward offers*. Conversely, **for apathy**, the regression slope for *reward* is shallower at LOW *effort* levels, and steeper at HIGH *effort* levels, whilst *effort* becomes less costly at HIGH *reward* levels. This manifests as a *reduction in choice for predominantly Low Reward (and to some extent Low Effort) offers*.



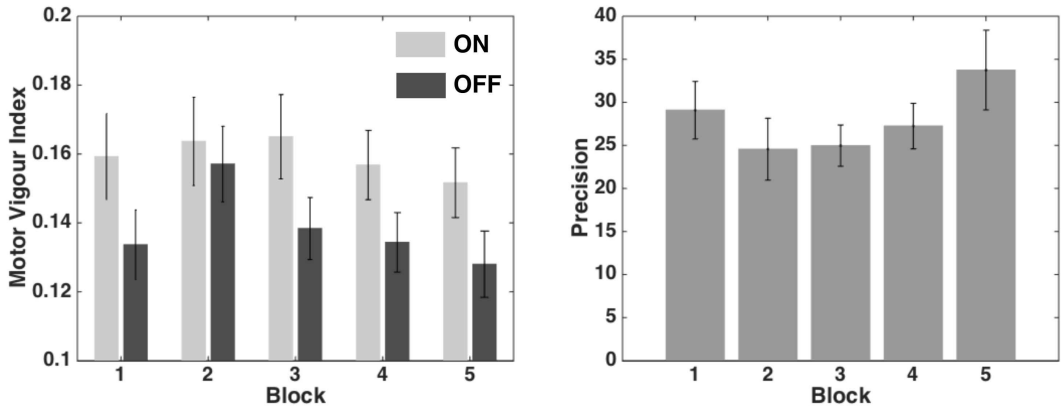
Proportion of offers accepted for each Reward level, as Effort level increases (**Top Panels**), and proportion of offers accepted, for each Effort level, as Reward level increases (**Bottom panels**).



Proportion of trials subjects failed to achieve force requirement. No differences between *ON & OFF groups* (mean difference (ON-OFF) = -0.002; paired t-test: t_{38} = -0.39, p=0.7); or *no apathy & apathy* groups (mean difference (no apathy – apathy) = -0.0195; unpaired t-test: t_{37} = -1.19, p=0.24).

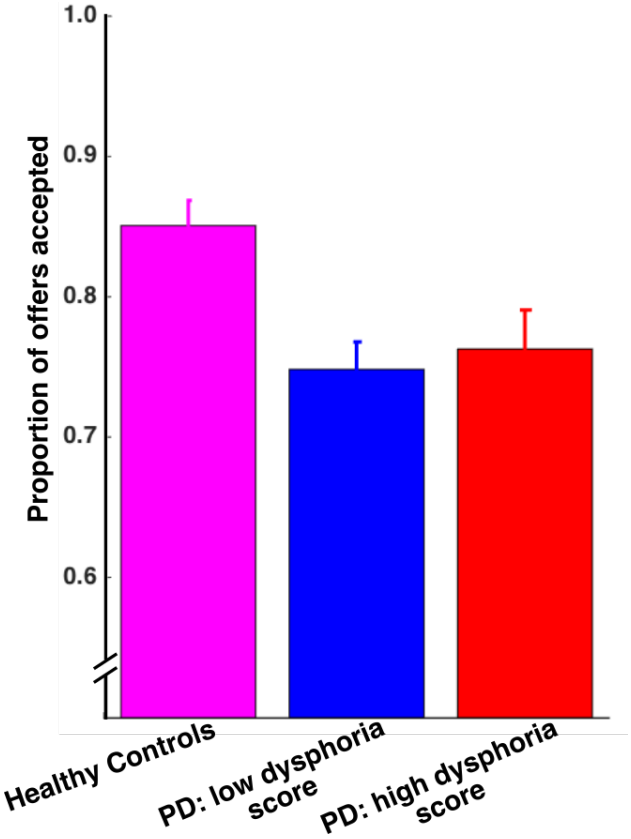


No evidence of changing acceptance rates across blocks. Proportion of offers accepted as reward increases plotted ON and OFF Dopamine, and for no apathy and apathy patients (in ON state). One-way ANOVA for main effect of block: ON Dopamine F(4,179) = 0.026, p=0.99; OFF Dopamine F(4,179) = 0.2, p=0.94; No apathy (ON) F(4,179) = 0.11, p=0.98; Apathy (ON) F(4,179) = 0.04, p=0.99).



Effects of Block on Motor Vigour and Precision.

There was a main effect of Block on motor vigour index: F(3.1,118)=3.4, p=0.02, **left panel**. Polynomial contrasts suggest this effect was not linear (p=0.26) but rather was a quadratic effect (p=0.036), with vigour increasing over the first half of the experiment before then reducing to baseline. There was a main effect of Drug (F1,38)=10.5, p=0.002), but importantly no drug * block interaction (F(3.1, 118)=0.98, p=0.41), meaning the observed reduction in motor vigour OFF dopamine was not dependent on the stage of experiment. There was no significant change in precision of motor responses (1/standard deviation) across the experiment, although there is a suggestion of a trend towards improvement in modulating response in the second half of the experiment (F(3,111.2)-1.92, p=0.13, **right panel**).



Higher scores on the dysphoria subscale of the BDI-II were not associated with reduced acceptance of offers ($t(34) = 0.29$, $p = 0.77$). Note groups were divided based on a median split of the data (cut-off subscale score = 4.5). BDI-II scores were not available for 3 patients.