Brain mechanisms underlying fatigue

and its impact on the motivation to exert effort

Tanja Müller

Department of Experimental Psychology

& New College

University of Oxford

A thesis submitted for the degree of

Doctor of Philosophy

in Experimental Psychology

Trinity Term 2021

Abstract

Fatigue, a feeling of tiredness or exhaustion, increases with effortful exertion and impacts motivation and performance. While healthy people typically recover during periods of rest, persistent forms of fatigue are a debilitating symptom in many medical conditions and in particular in Parkinson's disease (PD). To date, the neural and computational mechanisms in the brain that underlie fatigue and its impact on the willingness to exert effort are still poorly understood. Using physical effort-based decision-making paradigms and trial-by-trial self-report ratings in combination with a novel computational model, functional Magnetic Resonance Imaging and pharmacological manipulation, this thesis addresses the following outstanding research questions: How are brain systems implicated in effort-based decision-making impacted by momentary levels of fatigue in healthy individuals (Chapter 2)? Do people prioritise effort or reward information before option selection and are these preferences associated with fatigue and motivation to exert effort (Chapter 3)? How does fatigue develop as a function of effort, rest and rewards (Chapter 4), and what are the specific effects of dopaminergic medication in PD patients (Chapter 5)? Finally, how closely linked are dynamic changes in fatigue ratings and in the motivation to exert effort (Chapter 6)?

Together, the findings suggest that levels of fatigue fluctuate on a moment-to-moment basis as a function of the recent history of effortful exertion and rest, with underlying recoverable and unrecoverable components, impacting people's sensitivity to efforts and the subjective value of exerting effort to obtain rewards. Separate frontal sub-regions signalled recoverable and unrecoverable fatigue states, while current fatigue levels were integrated with value in the ventral striatum and the frontal pole. Dopaminergic medication affected self-reported fatigue, playing a differential role in recovery. In addition to these insights, the studies demonstrate that the paradigms and the computational model developed here may provide new approaches for the assessment and quantification of pathological forms of fatigue and associated deficits in motivation and might thereby help identify potential avenues for prevention and treatment.

This thesis contains approximately 52,000 words.

Acknowledgements

First, I would like to thank my primary and secondary supervisors, Dr. Matthew Apps and Prof. Masud Husain, for having taken me on as a DPhil student and I am deeply grateful for their guidance and support, for helpful feedback and for having been given the opportunity to take part in highly stimulating weekly lab meetings as well as to attend a range of national and international conferences and meetings and present and discuss some of this research there as well. Thank you, Matt, for inspiring discussions about experimental design, analyses, brain anatomy and the computational framework presented in this thesis and, not least, for conversations about science more generally during occasional lab outings to the pub. And thank you, Masud, for your valuable further advice on the research, project feasibility and time management.

Having had the privilege to be part of two research groups simultaneously for most of my DPhil, there are several people who have contributed to this work in some way or other and who have shaped my time in Oxford. Thank you to Sanjay, Sean, Pierre, Michele, Campbell, Yuen, Edwin, Lisa, Raquel, Younes, Youssuf, Liv, Annika and Dan as well as Anthony, Andrea, Seb and Marin, and to all other members of the Cognitive Neurology group and the Motivation and Social Neuroscience lab with whom I crossed paths over the years, for scientific and non-scientific discussions and advice, good humour and good company. I further wish to thank Miriam Klein-Flügge for her useful comments on the fMRI study and for teaching me some fundamentals of computational modelling, Mindaugas Jurgelis for helpful discussions on the fatigue ratings task, Ayat Abdurahman for her valuable support with data collection for the PD study, and Joseph Milton for his help with data collection for Chapter 4 (Experiments 1 and 3) and his contributions to the implementation of the online study.

I also owe many thanks to all of the research participants. Without their time and efforts, this kind of research on fatigue and motivation in humans would not have been possible.

In addition, thank you to the other DPhil students in the Department of Experimental Psychology for sharing this journey and for occasional catch-ups even when we were suddenly separated for some time following the Tinbergen Building closure. And thank you to my friends at New College and the wider university for wonderful dinners, celebrations and inspiring conversations over the past few years.

Thanks to my house mates, Antonin, Idil and Lottie, for further introducing me to British, Cypriot and French culture, for pleasant conversations and insightful discussions about PhD life, science, human relationships, Brexit and climate change, for helping me keep my bike in good working order and for delicious Christmas dinners with and without electricity.

I am very thankful to my parents for their encouragement and their general support during my studies and in particular during the pandemic. A special thanks goes to my mum for making sure I did not forget to take short breaks and engage in physical activity during the final stage of my DPhil. And thank you to my family in general, including my grandmother and my godfather, for their warm welcomes whenever I came back for a visit.

Finally, I am extremely grateful for the financial support I received through scholarships from the German Academic Exchange Service (DAAD) and the German Academic Scholarship Foundation (Studienstiftung des deutschen Volkes) as well as through the Funds for Women Graduates (FfWG) from the British Federation of Women Graduates, which allowed me to pursue my DPhil studies at Oxford and to undertake this research.

Table of Contents

1 General Introduction

1.1 Fatigue: a common but poorly understood phenomenon

Why do we feel tired after demanding tasks or exercise, and how does this affect our motivation, behaviour and performance? Why are some people more fatigued than others, and why do some persist while others decide to take a break or give up? For more than 100 years, physiologists and psychologists have been puzzled about how tiredness following activity, or *fatigue*, arises and how periods of work and rest affect people's ability and willingness to continue to work (e.g. Mosso et al., 1904; Thorndike, 1912). Yet, there is still much debate and a lack of clarity around the role of fatigue and the factors modulating it.

Over the past years, the phenomenon of fatigue has increasingly attracted attention of scientists, economists, physicians and the general population. Surveys from the Netherlands and the US suggested that about a quarter to a third of the working population feels fatigued most of the time (Bültmann et al., 2002; Ricci et al., 2007), and fatigue is reported as a symptom in a quarter of primary care appointments in Ireland (Cullen et al., 2002). While considered a normal experience in general that arises through exertion and declines through taking rests, with impacts on behaviour, performance and productivity (Borghini et al., 2014; van Dijk and Swaen, 2003), it can also take on more severe and persistent forms associated with pervasive reductions in daily activity. In those cases, the phenomenon has sometimes been described as Chronic Fatigue Syndrome or as one symptom alongside others in a broad range of clinical conditions (Wessely, 2001). Indeed, such elevated levels of fatigue are very commonly observed in various neurological and psychiatric disorders like Parkinson’s disease, stroke, multiple sclerosis and major depression (Chaudhuri and Behan, 2004; Demyttenaere et al., 2005; Friedman et al., 2016; Lerdal et al., 2009, 2007; Skapinakis et al., 2003) as well as in cancer patients (Ryan et al., 2007) and after viral infection (e.g. Townsend et al., 2020).

As multidimensional as the concept of fatigue is, as diverse are the research approaches aiming to address it and the aspects they are focusing on (Kluger et al., 2013). Theoretical accounts and research studies have mostly differentiated fatigue in terms of where in the body changes occur that may be associated with it (*peripheral* versus *central* fatigue) (Chaudhuri and Behan, 2004; Kluger et al., 2013; Tanaka and Watanabe, 2012) as well as according to what kind of activity induced it (*cognitive*/*mental* versus *physical*/*motor* fatigue), although the latter distinction is sometimes also used to distinguish between certain factors or effects that may contribute to or result from fatigue (Boksem and Tops, 2008; Chalder et al., 1993; Chaudhuri and Behan, 2004; Friedman et al., 2016; Hockey, 2011; Inzlicht and Marcora, 2016; Kurzban et al., 2013; Lou, 2009; Smets et al., 1995; Tanaka and Watanabe, 2012). Distinctions have also been made between rather general and persistent levels of fatigue (*trait* fatigue) and a current fatigue state which waxes and wanes over the course of a task or over the course of a day or week (*state* fatigue), yet the timescales for these definitions vary considerably. This distinction has been made explicitly in some work (e.g. Calderwood and Ackerman, 2011; Genova et al., 2013; Müller and Apps, 2019) and implicitly in much of the above reported literature.

Despite these diverse efforts to unravel the phenomenon, many questions remain. Crucially, it is still unclear how fatigue develops, how it affects behaviour and which brain mechanisms underlie it. In this thesis, I will mainly focus on the computational and neural mechanisms in the brain underlying the development of fatigue during effortful tasks, or state fatigue, and its relationship to dynamic changes in the willingness to exert effort for rewards. While physically demanding tasks are used in the experiments reported here, in the general introduction and the general discussion I will also point to some theoretical accounts and experimental work on cognitively demanding tasks in order to highlight potential overlapping as well as distinct mechanisms.

1.2 Fatigue and behaviour

1.2.1 Effects of effortful exertion on fatigue

Fatigue is classically thought to arise through effortful exertion, with higher levels of effort increasing the rate of fatigue build-up (Boksem and Tops, 2008; Carroll et al., 2017; Tanaka and Watanabe, 2012). Researchers have related increases in fatigue and its impact on behaviour to an increased subjective perception of effort during different types of exercise (de Morree and Marcora, 2013; Marcora, 2009; Pageaux, 2016; Pageaux and Lepers, 2016). As such, mechanisms involved in generating effort likely also play a role in the experience of fatigue.

On the contrary, fatigue is expected to subside after rest, while this has mostly been inferred from the fact that cognitive and motor performance improves post versus pre resting (Carroll et al., 2017; Helton and Russell, 2015; Mackworth, 1964; Tucker, 2003) and people decide to resume their work again (Meyniel et al., 2014, 2013; Meyniel and Pessiglione, 2014). In addition, theoretical accounts of fatigue in brain disorders suggested that in persistent forms of fatigue, in particular the recovery is impaired (Chaudhuri and Behan, 2004).

While this research suggests that effort and rest are crucial factors for the development of fatigue, there has been less agreement on the underlying mechanisms and on other processes that might potentially play a role. During fatiguing tasks and during recovery, changes to the autonomic (e.g. cardiovascular) system have long been noted, in particular in the case of physical exertion (Micklewright et al., 2017; Williamson et al., 2006) but potentially also in the case of prolonged cognitive exertion (Fairclough and Mulder, 2011; Gendolla et al., 2012). However, there is an ongoing debate on the role and relative contribution of peripheral versus central systems to perceived effort and fatigue, mostly when physical effort is exerted (Carroll et al., 2017; Marcora, 2009; Noakes, 2012; Nybo and Secher, 2004; Tanaka and Watanabe, 2012). In addition, the role of glucose consumption or “resource depletion” in respective systems has been a topic of scientific discourse, primarily when exerting mental effort or cognitive control over time (Hockey, 2011; Inzlicht and Schmeichel, 2012; Kurzban, 2016; Kurzban et al., 2013; Muraven and Baumeister, 2000; Shenhav et al., 2017) but also during physical exercise and fatigue (Marcora, 2009; Nybo and Secher, 2004).

To date, the relative contributions and dynamics of the different processes and systems remain somewhat unclear and seem to also depend on the type, intensity and pattern of exertion (Weir et al., 2006). Nevertheless, the evidence suggests that doing demanding tasks and taking rests might induce and recover fatigue, respectively, over time. However, studies have typically asked participants to rate their perceived exertion or perceived effort rather than directly assessing feelings of fatigue, collected ratings over long intervals such as before and after exercise or a demanding task and sometimes in between longer blocks of the task. Moreover, although fatigue is putatively induced by effortful exertion, experiments rarely vary systematically the amount of effort required (de Morree and Marcora, 2013; Lohse and Sherwood, 2011; Marcora et al., 2009; Parry et al., 2011). Therefore, it is unclear the extent to which fatigue develops through effortful exertion and to which it can be dissociated from other factors such as for example time-on-task or boredom.

1.2.2 Effects of fatigue on performance[1]

Decades of empirical research have suggested that fatigue leads to reductions in task performance, or at least that fatigue and reduced performance co-occur. Often, decreased performance in the course of a task is even used as the defining feature of state fatigue, although this could just as easily be accounted for decrements in sustained attention irrespective of fatigue (Boksem et al., 2005;

[1] Most parts of this section have been published in the meantime (Müller, T., Apps, M.A.J., 2019, *Neuropsychologia*). Permission to include the material in this thesis has been given.

Lim et al., 2010; Tanaka et al., 2014; Mackworth, 1964). In cognitive tasks, fatigue effects are typically characterised as a slowing in reaction times and declines in task accuracy over time. These effects occur in tasks designed specifically to probe the mechanisms underlying fatigue (Boksem et al., 2006; Mackworth, 1964; Tanaka et al., 2014), which typically average outcome measures across a subset of trials or a certain time window, but are also observable across many classical cognitive tasks.

Early investigations that reported decrements in performance over time included perceptual sensitivity and threshold assessments as well as tasks examining vigilance or high-speed perceptual motor performance (Mackworth, 1964; Nuechterlein et al., 1983; Shalev et al., 2011; Warm et al., 2008). Similar time-on-task effects have also been reported in the case of physical exertion (Carroll et al., 2017; Marcora, 2009; Meyniel et al., 2014; Tanaka and Watanabe, 2012), including studies which required participants to execute physical force (e.g. grip force) as well as those which examined exercise (e.g. endurance) performance. For example, during sustained maximal force exertion, activation of muscles and the exerted force or power decline over time (Enoka et al., 2011; Sidhu et al., 2013; Vøllestad, 1997). In addition, extended effortful exertion on one task can impact performance on another type of task (Inzlicht and Schmeichel, 2012; Shigihara et al., 2013; Van Cutsem et al., 2017), which has been taken as evidence that exertion, and possibly fatigue, may impact on some domain-general process such as motivation (Müller and Apps, 2019).

Although much of the literature has focused on how performance changes with *time-on-task*, several studies support the notion that such changes are not just a function of time-on-task but rather depend on the difficulty or the effort required. A greater degree of difficulty in a cognitive task (e.g. greater cognitive load or more difficult perceptual discrimination) can lead to more rapid declines in performance (Boksem and Tops, 2008; Mackworth, 1964; Warm et al., 2008). A similar effect of effort level has been observed in the physical domain. When, instead of sustained maximal force, submaximal force is required, i.e. only a proportion of the maximal force an individual is able to produce, perceived effort still somewhat increase but there is less of a decline in muscle output (de Morree et al., 2014; Marcora, 2009). Relatedly, performance in both cognitive and physical tasks tends to improve after periods of rest (Carroll et al., 2017; Helton and Russell, 2015; Mackworth, 1964; Tucker, 2003).

Together, these lines of research show that effort and rest affect both fatigue and performance, suggesting that changes in performance, or at least changes in performance over time, could be used as an index of fatigue or as an objective measure of fatigue and that potentially fatigue might affect performance. However, changes in performance may not equate to changes in fatigue (e.g. Ackerman et al., 2010; Benoit et al., 2019).

1.3 Fatigue and motivation

1.3.1 Effects of motivation on fatigue

Further work has suggested that psychological factors such as someone's current level of motivation and focus of attention, which in turn depend on both internal processes and external stimuli such as for example potential incentives, may modulate fatigue (Bigliassi, 2015; Boksem and Tops, 2008; Hockey, 2011). In the literature on cognitive effort and fatigue, some researchers even proposed that perceived fatigue is a result of or a by-product of the potentially subconscious analyses of the predicted costs and benefits associated with exerting effort (Boksem and Tops, 2008; Wylie et al., 2017), and that the feeling of effort may stem from the decision to exert effort (Bijleveld, 2018). Somewhat similar mechanisms have also been proposed by some researchers to explain fatigue and interindividual differences in fatigue during physical exercise (McMorris et al., 2018; St. Clair Gibson et al., 2003).

For instance, in a modified version of the Simon task, a task examining the effects of the congruency of locations of stimuli and responses, task performance as reflected in reaction times and error rates tended to decline over the course of the experiment (Boksem et al., 2006). Yet when 20 minutes before the end of the task participants were told that their performance would be compared with other participants' performance and the best performing participants would receive 25 Euros extra, increases in accuracy and response speed were observed in many participants. These results provided support for the idea that additional rewards and thus increased motivation can counteract performance declines that might be linked to fatigue, although fatigue was not assessed explicitly.

Relatedly, in a prolonged n-back task that taxes working memory, decreased performance and decreased pupil diameter – typically an index for psychophysiological arousal – as well as increased subjective fatigue ratings were observed with time-on-task, as measured over blocks of trials. But when participants were given the incentive that the remaining duration of the experiment would depend on their performance relative to previous blocks, all measures improved (Hopstaken et al., 2015). Yet, while being interpreted as an additional incentive, this experimental manipulation could similarly be interpreted as a reduction in the delay cost, i.e. in the time until the goal (end of experiment) is reached. As such, the particular effect of motivation on self-reported fatigue remained somewhat uncertain.

Furthermore, research on physical exercise over the past four decades has pointed out that the perception of exertion is dependent on the actual work performed but to some degree may also depend on psychological factors and be modulated by attentional processes, especially when physical demands are not too high (Bigliassi, 2015; Blanchfield et al., 2014; Boutcher and Trenske, 1990; Lohse and Sherwood, 2011). Motivational self-talk for example was found to reduce ratings of perceived exertion after a cycling exercise and to enhance endurance performance (Blanchfield et al., 2014). Some other work also points towards potential links between exertion, subjective perceptions of effort, motivation and fatigue. Findings from a study in which participants cycled on an ergometer were taken to suggest that tolerance for high-intensity aerobic exercise in highly motivated people is limited by the perception of effort rather than directly by physiological changes in the muscles (Marcora and Staiano, 2010), i.e. people may stop working even before they are completely exhausted. And in studies using grip force as a manipulation of effort, monetary rewards have been found to affect people's decisions to work and their respective behaviour (Meyniel et al., 2014, 2013; Meyniel and Pessiglione, 2014).

This multitude of theories and findings overall stresses the contribution of processes beyond the muscles and the peripheral nervous system to fatigue and its effects on behaviour. In particular they suggest that motivation may play a crucial role for explaining the effects of fatigue on performance and that perhaps fatigue might also be under the influence of motivation. However, for example the question of whether and how benefits, such as rewards, and thus motivation might impact on an individual's perception of fatigue has rarely been examined systematically.

1.3.2 Effects of fatigue on motivation

Following observations that both fatigue and performance may change over time and scientific proposals that both could be impacted by motivational processes, it has been suggested that the effects of fatigue might be closely linked to motivation and that exerting effort could lead to a reduction in the subsequent willingness to allocate effort (Boksem and Tops, 2008; Hockey, 2011; Kurzban et al., 2013; Marcora, 2008; Tanaka and Watanabe, 2012). Yet very few studies have systematically addressed and examined the underlying cognitive and neural mechanisms. In the following, I will first outline one approach by which motivation can be examined and quantified and will then develop a theoretical framework for how fatigue may impact on the motivation to exert effort.

1.3.2.1 Cost-benefit decision-making as an index for motivation

Motivation, sometimes defined as the processes that determine the direction and energization of behaviour (Elliot, 2006), is often characterised as being underpinned by evaluations of whether an action, or an action sequence, is worth it (Balleine and O'Doherty, 2010; Salamone et al., 2016). According to prominent theories, costs such as the effort associated with an action are usually kept minimal and only tolerated to the degree that is necessary for goal attainment. Cost-benefit evaluations are thereby thought to have a considerable impact on people's motivation and levels of activity (Brehm and Self, 1989). Such valuations are highly subjective and are dependent on how effortful people perceive possible actions to be. Using decision-making paradigms in which the magnitude of reward offered and the amount of effort required to obtain the reward are experimentally manipulated over a series of trials, the results of some recent studies supported the idea that effort costs discount people's subjective valuations of rewards and thus their invigorating and incentivising effects, leading to drops in motivation (Apps et al., 2015; Bonnelle et al., 2015; Chong et al., 2017; Hartmann et al., 2013; Klein-Flügge et al., 2015; Kool et al., 2010; Le Heron et al., 2018a; Shenhav et al., 2013; Studer and Knecht, 2016; Verguts et al., 2015; Westbrook et al., 2013). It has been suggested that these kinds of paradigms are also well suited for probing such *effort discounting* effects and alterations in motivation in neurological and psychiatric conditions (Chong et al., 2016; Husain and Roiser, 2018; Pessiglione et al., 2018) and possibly for quantifying potential effects of fatigue on motivation (Massar et al., 2018).

While many studies focus on the decision-making process at the time a choice is being made, some other lines of work which tracked participants' eye positions, but which however did not investigate cost-benefit decisions, suggested that attentional mechanisms prior to option selection may be relevant and can predict choices (Fisher, 2017; Krajbich et al., 2010). Very recently, similar mechanisms have been observed during an effort-based decision-making task in which participants were required to decide whether to expend cognitive effort (n-back task) in order to obtain rewards. Using participants' gaze behaviour and computational modelling, they inferred that attention to reward versus effort information early in the decision-making process was associated with decisions to work and related this bias to individual dopamine availability in the striatum (Westbrook et al., 2020).

Notably, options – oftentimes two – are presented simultaneously in many of these kinds of tasks. Yet, some work suggests that presentation order, and possibly presentation duration, might be relevant and influence decisions. This has for example been shown in a study in which participants made a series of choices on whether to perform arithmetic calculations that varied in the level of effort required (easy versus hard) and in the magnitude of reward offered (small versus large) (Vassena et al., 2019). Here, information about the difficulty of the task and the magnitude of the reward (points) on offer was presented *consecutively*, with the first cue presented for a longer duration than the second one. The researchers found that when reward information was presented first, people were more likely to accept the offer. But comparison of choice behaviour with a condition in which both pieces of information were presented *simultaneously* suggested that people in general tend to prioritise effort information during decision-making. However, it remained unclear whether similar processes apply when people, instead of being externally cued, decide themselves which piece of information they want to look at first and which factors might be associated with such potential preferences.

Together, this collection of work demonstrates that effort-based decision-making paradigms can be useful to probe motivational processes. In addition, it suggests that costs and benefits may be weighed differently in these decisions, as internal and external factors prior to option selection change. Given the previous work linking effort and fatigue, it could be assumed that fatigue may be an internal factor that affects effort-based decisions, but motivation may also be impacted as external factors change.

1.3.2.2 Computational models of effort discounting

Research examining effort-based decisions often uses computational modelling to specify and quantify how willing to exert effort for rewards someone is. In these models, the (subjective) value a person ascribes to different combinations of effort and reward is typically calculated. Such *discounting models* are mathematical functions that aim to predict participants' behaviour, with some advantages over traditional statistical techniques (Corrado and Doya, 2007; Mars et al., 2012).

In particular, computational modelling allows specification of the processes thought to be involved in participants' performance or in their responses, based on theory and empirical evidence, in a mathematically precise form. Not only can task parameters and participant characteristics be combined but computational models are also well suited for testing processes spanning over multiple trials and for identifying factors that shape the development of latent, not directly measurable, variables over time. They usually contain a number of free parameters that capture and quantify the influence of a specific process or variable on information processing and behavioural output such as performance, a choice or a rating. These parameters are estimated from the data, with parameter values adjusted until the pattern of output that they create matches the participant's behaviour or responses as closely as possible. By assessing and comparing the fit between the data and different models, this approach can help to provide a better understanding of the mechanisms underlying cognition, perception and behaviour as well as to identify specific processes that differ in psychiatric or neurological conditions or that may be responsive to particular treatments (Adams et al., 2016; Corrado and Doya, 2007; Mars et al., 2012).

In the effort-discounting literature, different mathematical functions have been fitted to participants' choices depending on the type of task, reward and effort (Chong et al., 2017; Hartmann et al., 2013; Klein-Flügge et al., 2015; Lockwood et al., 2017; Prévost et al., 2010), with the shape of each function reflecting how an increase in effort impacts on choices. For example, linear models would predict that with increasing effort, a participant's subjective value of the reward offered is discounted in a constantly increasing manner, whereas hyperbolic models would predict that changes at lower levels of effort have a relatively greater impact on changes in subjective value than changes at higher levels of effort, and parabolic models (see **Figure 2**, section 1.3.2.3, for an example) would assume the opposite case. In effort-based decision-making tasks very similar to the ones that will be used in this thesis, in which participants were given two options on every trial, namely i) a work option that varied over trials in the magnitude of monetary reward offered and the amount of isometric force required to obtain the reward and ii) a fixed rest option for a low reward, a parabolic function has been found to fit participants' choice behaviour better for physical effort than other functions (Chong et al., 2017; Hartmann et al., 2013; Lockwood et al., 2017).

As such, using these tasks together with computational modelling approaches, trial-by-trial estimates of the subjective value of options can be obtained and predictions about the decision process be made. The trial-by-trial estimates could for instance also be correlated with neural activity to identify whether and where in the brain there are neural processes similar to the ones specified in the model (Corrado and Doya, 2007; Mars et al., 2012). Notably, however, the effort-based decision-making studies described above did not assess potential effects of fatigue, or they controlled for potential effects of fatigue by having participants perform the effort of the work offer they had chosen only on a subset of trials or even only after the experiment. Therefore, whether and how fatigue may impact on effort-based decisions has largely remained unclear.

1.3.2.3 Fatigue and its impact on effort-based decisions: Core mechanisms?

Despite long being posited, until recently, little work examined how fatigue might impact on the willingness to exert effort. One study for example investigated how people chose to take rests as a function of the grip force they had exerted within a certain time interval, while the reward obtained was proportional to the time spent above a given force level. They proposed that decisions to stop and resume effort to attain rewards are guided by a cost evidence accumulation signal, presumably linked to fatigue, which reaches upper and lower boundaries (Meyniel et al., 2013). Other lines of research also looked at how cost-benefit decisions might be affected by recently exerted effort and thus possibly by fatigue, but instead of investigating effort-based decisions the researchers were interested in examining how people traded off rewards against time and how willing they were to wait for rewards. They found that over a whole day of performing a demanding working memory task, people more and more favoured smaller, immediate monetary rewards over lager, delayed rewards (Blain et al., 2016). Relatedly, in another study, overtrained, fatigued triathletes tended to be biased towards favouring immediate over delayed monetary rewards in economic choices (Blain et al., 2019). A recent investigation, in which decisions on the expenditure of physical effort (time cycling on an ergometer) to obtain rewards had to be made, further suggested that people might be biased towards avoiding high effort after compared to before exhaustion, as inferred from kinematic analysis of participants' mouse movements when they were deciding whether to exert effort or rest (Iodice et al., 2017a). This provides evidence for the assumption that previous efforts, and possibly fatigue, can impact on decision-making processes.

However, mechanistic neurocognitive accounts of how fatigue develops during a task or over repeated exertion remain scarce. Building on the existing accounts and the experimental work outlined above and in the previous sections, I am putting forward a theoretical framework for how the recent history of effortful exertion, and thus fatigue, impacts on the subsequent motivation to exert effort (Müller and Apps, 2019). Within this framework, effortful exertion leads to fatigue. Fatigue is continuous and changes moment-to-moment, increasing depending on the amount of effort exerted and decreasing depending on the time spent resting (**Figure 1**).

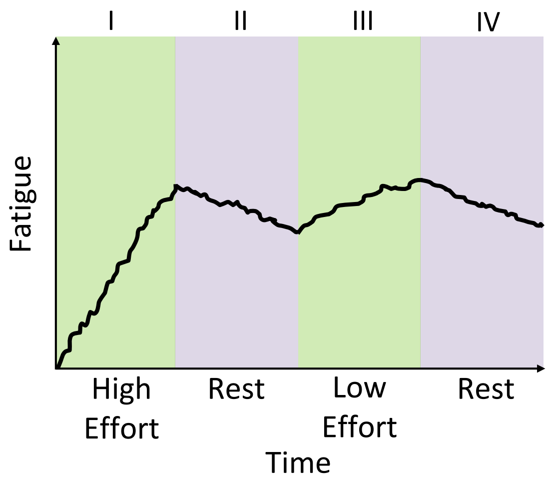

Figure 1. **Schematic representation of predicted effects of effortful exertion and rests on fatigue in a task.** Fatigue increases as effort is exerted (I and III) and decreases with rests (II and IV). Higher levels of effort increase the rate of fatigue build-up (see I versus III). The figure was produced by myself and has been published in Müller and Apps (2019).

It is further proposed here that fatigue increases people's weighting of effort costs, leading to greater discounting of rewards associated with performing a cognitively or physically demanding task as fatigue increases such that the subjective value of exerting effort into a task and thus motivation might decline (**Figure 2**). As a result, unless a higher reward is offered, the effort might not be considered "worth it" anymore and people become more likely to choose to take a break or switch to a different kind of task that they feel is currently less effortful or more rewarding.

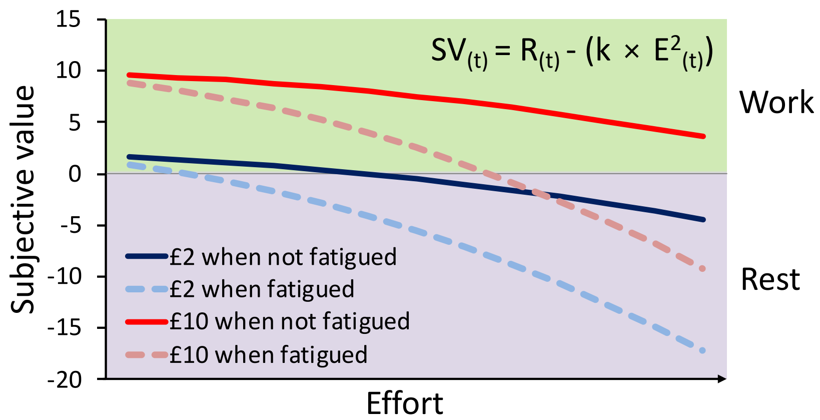

Figure 2. **Predicted effects of fatigue on the subsequent motivation to exert effort for rewards.** The subjective value (SV) of a reward (R) at any given time (t) is discounted by the expected effort (E) required to obtain the reward. The degree to which someone discounts rewards by effort is dictated by a discount parameter (k), with higher values reflecting greater devaluation of rewards. Note that the depicted function is based on previous work on effort-based decision-making that provided evidence for a parabolic model of effort-discounting when decisions about physical effort expenditure are made (Chong et al., 2017; Hartmann et al., 2013). Fatigue, as illustrated in the dotted lines, increases people's weighting (k) of effort costs, thereby further decreasing the value of exerting effort, particularly with high effort demands. When the expected costs outweigh the expected benefits, people are likely to rest or to switch to an alternative course of action. Fatigue therefore serves to make efforts previously ascribed high value now have lower subjective value and be considered "not worth it". The figure which I co-produced has been published in Müller and Apps (2019).

If people, however, still continue with the task, their performance such as the accuracy or vigour of actions may decrease. This framework of fatigue and motivation changing moment-to-moment will be used and tested throughout this thesis.

1.4 Neural basis of fatigue[2]

A look at the neural processes in the brain might help to better understand the mechanisms underlying fatigue and the role of motivation. Although some theoretical accounts suggest that neural mechanisms in the brain are crucial for the emergence of fatigue during exertion (Noakes, 2012; Nybo and Secher, 2004; St. Clair Gibson et al., 2003; Tanaka and Watanabe, 2012) and in several clinical conditions (Chaudhuri and Behan, 2004; Dobryakova et al., 2013; Kuppuswamy, 2017; Stephan et al., 2016; Tanaka et al., 2013), our understanding of these mechanisms is still limited as there is little empirical work specifically aimed at identifying the relevant brain systems and processes. This may partly be due to the fact that neural signatures of fatigue seem difficult to isolate from potentially correlated factors. For example, fatigue inferred from neural correlates of fluctuations in performance might be confounded with other effects, and neural correlates of self-reported fatigue might potentially largely overlap with neural systems generally involved in interoception and introspection if those self-reports

[2] Most parts of sections 1.4.1, 1.4.2 and 1.4.3 have been published in the meantime (Müller, T., Apps, M.A.J., 2019, *Neuropsychologia*). Permission to include the material in this thesis has been given.

are not collected frequently such as on a trial-by-trial basis and if fatigue is not induced and manipulated systematically. In addition, neurological patients suffering from fatigue are oftentimes also affected by various other symptoms and underlying comorbidity (Friedman et al., 2007; Skorvanek et al., 2015), which may make it difficult to attribute alterations in brain structure and function specifically to fatigue. Despite these complexities, such investigations can give some initial clues about the brain mechanisms underlying fatigue and its influence on motivation and behaviour.

1.4.1 Correlates of fatigue in physical tasks

In many tasks, reductions in activity over time might be – at least partially – predictive of a failure to continue to exert the required effort. Although such measures are only a proxy of fatigue and motivation, they can be useful for identifying candidate regions that are under the influence of fatigue. There are broadly three different systems in which activity seems to change with time on task, or with sustained grip force, suggesting that they might be linked to fatigue.

Studies probing the neuroanatomical basis of physical fatigue have used functional Magnetic Resonance Imaging (fMRI), Positron Emission Tomography (PET), Electroencephalography (EEG) and Magnetoencephalography (MEG) to identify the systems in the brain in which neural activity parallels behavioural changes presumably associated with fatigue. Firstly, these studies show that during sustained exertion or when examining pre and post physically demanding tasks, there are changes in Cerebral Blood Flow (CBF) and BOLD signals in the primary motor cortex, premotor cortex and the supplementary and pre-supplementary motor areas, as well as in EEG components arising from sensorimotor systems (Avanzino et al., 2011; Hou et al., 2016; Kuppuswamy, 2017; Liu et al., 2002; Meyniel and Pessiglione, 2014; Tanaka and Watanabe, 2012; van Duinen et al., 2007). In one MEG study, Meyniel and Pessiglione (2014) specifically aimed to examine how incentivisation influences choices to spontaneously exert grip force or take rests and its links to the motor system. They found that beta-synchronisation in the motor system was linked to how long people spent taking a period of rest during trials and also to how much money was on offer on the trial. In doing so, they directly tied in signals from the motor system with people's willingness to exert physical force for reward. Other work has shown that signals from premotor and motor areas are linked to increases in the perception of physical effort during demanding tasks (de Morree et al., 2014; Marcora, 2009). Together, they all highlight that activity in motor and sensorimotor systems may be susceptible to fatigue.

Secondly, changes in activity over time have been observed in areas that are thought to play important roles in processing internal bodily signals (Ainley et al., 2016; Craig, 2003). This includes the somatosensory cortical areas and posterior and mid portions of the insula that process interoceptive as well as exteroceptive signals from the muscles (Liu et al., 2002; Meyniel et al., 2013; Tanaka and Watanabe, 2012). For example, Meyniel and colleagues took a somewhat different approach and used MEG and fMRI to examine how people choose to take rests as a function of the effort they have exerted on a handgrip across a 30-second time interval during which the monetary reward obtained was proportional to the time spent above a given force level. Here, the effort level was not made explicit before the start of the trial such that participants had to experience the cost and adjust their behaviour accordingly. Analyses of MEG data identified signals steadily increasing and decreasing during effort and rest respectively, and in the fMRI data, activity in the posterior insula correlated with a theoretical cost evidence accumulation signal, potentially linked to fatigue (Meyniel et al., 2013).

Finally, there are additional fluctuations in activity in other areas. Posterior portions of the anterior cingulate cortex (ACC), insula and dorsolateral prefrontal cortex (DLPFC) are granular and have direct projections to the spinal cord and are often considered part of the motor system (Mufson and Mesulam, 1982; Palomero-Gallagher et al., 2008; Petrides and Pandya, 1999). However, a large number of studies examining fatigue finds activity in regions lying more rostral and anterior, regions that through their anatomical properties are more likely to be involved in cognitive processing (Haber and Knutson, 2010; Parent and Parent, 2006). Research using either EEG or fMRI has shown respective dynamics in activity in anterior portions of the midcingulate cortex (MCC), or anterior cingulate sulcus (area 24c'/32'), in the anterior portions of the insula (AI; area idg), and in portions of DLPFC putatively in areas 46 and 9/46 (Liu et al., 2002; Marcora, 2009; Tanaka and Watanabe, 2012). Increases in activity in these regions have also been linked to parallel increases in ratings of the perception of effort when submaximal forces are exerted (Williamson et al., 2006).

In sum, these studies highlight that there are systems beyond those directly involved in motor control in which changes in activity are associated with changes in behavioural outputs and in the perception of effort during demanding tasks. This pattern of activity somewhat fits with a profile one would expect to be linked to fatigue, suggesting that these systems might potentially play a role in the development of fatigue.

1.4.2 Correlates of fatigue in cognitive tasks

Research examining the neural basis of cognitive fatigue has used a variety of (cognitive) tasks and mainly looked for variability in neural activity and associated changes in performance. Much like in tasks requiring physical exertion, fluctuations in activity have been observed in brain areas that appear to relate to the specific task or cognitive operations. For instance, studies that required sustained attention showed decreased activity in lateral frontal and parietal areas which are well known for their roles in attentional control as well as in visual cortical areas over time (Asplund and Chee, 2013; Boksem et al., 2005; Borghini et al., 2014; Lim et al., 2010; Tanaka et al., 2014, 2006). In EEG studies using the Simon task, changes in performance and ratings of fatigue were linked to a decreased amplitude of EEG components linked previously to the cognitive operations required for the task (Boksem et al., 2006; Möckel et al., 2015).

In addition, alterations in neural activity with cognitive fatigue have also been noted in the same areas as those that change with physical fatigue. Using arterial spin labeling during a continuous psychomotor vigilance test, Lim et al. (2010)

found decreases in activity in DLPFC, in the dorsal ACC (dACC) and in the AI (see also Asplund and Chee, 2013). Similarly, performance in visual attention tasks, as indexed by reaction times, misses and false alarms, was found to decrease, while theta and lower-alpha EEG band power – typically negatively correlated with arousal levels – increased with time-on-task and was related to ratings of task aversion (Boksem et al., 2005). Analysis of event-related potentials (ERPs) indicated modulations of components that are typically localised within medial prefrontal cortex and particularly in the ACC (Boksem et al., 2005; Boksem and Tops, 2008; see also Grinband et al., 2011). Likewise, action monitoring performance and response preparation decreased in a modified version of the Simon task over the course of the experiment, as indicated by increased reaction times, standard deviations of reaction times, and error rates as well as a decrease in Ne/ERN, N2 and CNV amplitudes, ERPs localised in the dACC (Boksem et al., 2006; Boksem and Tops, 2008; Möckel et al., 2015; see also Lorist et al., 2005). Beta band power from medial frontal cortex has also been linked to time-on-task effects between trials that are restored after rests in non-human primates (Wilson et al., 2016). Another study assessed fatigue in a working memory (n-back) task more directly by collecting ratings of fatigue before and after each block of the task. They found that self-reported fatigue was associated with activity in dACC and pre-supplementary motor area as assessed by fMRI, but also noted that there was no simple one-to-one mapping between changes in self-reported fatigue, in performance and in brain activity (Wylie et al., 2017).

Overall, this literature reveals that exerting cognitive effort is accompanied by decreased performance and neural changes, putatively linked to fatigue, in various cortical areas and in particular in the dACC. Moreover, recent research in a sample of elderly participants suggested that, across different cognitive tasks, interindividual differences in the subjective experience of fatigue resulting from cognitive work correlated with interindividual differences in right insula- and putamen-based network connectivity patterns (Anderson et al., 2019). This would suggest not only a role of the insula but also of the dorsal striatum and connected regions in cognitive fatigue. Notably, however, self-report ratings were only taken before and after the tasks, there was no specific differentiation between different fatigue-associated questionnaire items, and fatigue scores and activity patterns were not specifically related to task properties, participant performance or performance outcomes. As such, while demonstrating potential general processes across cognitive tasks, the precise neural mechanisms and roles of these regions in fatigue remained somewhat unclear.

1.4.3 Brain regions linked to interoception, metacognition and monitoring

The three regions emphasised in the previous sections, namely the AI, DLPFC and dACC, have also been implicated in monitoring *internal states*, albeit in different forms. Such monitoring of internal states highlights them as candidates for monitoring fatigue-related changes in other brain systems.

AI function has long been linked to interoceptive awareness and the degree to which one is sensitive to changes in the internal states of one's body (Ainley et al., 2016; Craig, 2003). This has been demonstrated in a number of studies in which the structure and function of the insula correlate with people's ability to detect and be aware of their own heartbeats (Ainley et al., 2016; Critchley et al., 2004). Other investigations have also related AI to the perception of effort during task performance and to central cardiovascular control during exercise (Otto et al., 2014; Williamson et al., 2006) as well as to the conscious perception of errors and associated autonomic responses (Ullsperger et al., 2010).

DLPFC is commonly implicated in studies examining introspection and metacognitive abilities (Fleming et al., 2010; Fleming and Dolan, 2012; Stephan et al., 2016). That is, how consciously aware individuals are of their errors during cognitive tasks is related to the structure and function of the DLPFC. People's accuracy at reporting, and confidence in, their performance in cognitive tasks has been linked to grey matter volume and also to responses in the DLPFC during the performance of perceptual decision-making tasks requiring cognitive control (Fleming et al., 2010; Fleming and Dolan, 2012). This would point to the DLPFC as monitoring information about the performance or state of other systems, and perhaps therefore suggest its role in processing information about fatigue-related changes in task-dependent systems.

The dACC is also linked with interoception, autonomic responses, and the monitoring of performance (Amiez et al., 2013; Botvinick and Braver, 2015; Critchley et al., 2004; Danielmeier et al., 2015; Fairclough and Mulder, 2011; Fleming and Dolan, 2012; Magno et al., 2006; Procyk et al., 2016; Ridderinkhof et al., 2004; Sarter et al., 2006). For many years it has been shown that the dACC signals errors in cognitive tasks, and its function has been linked to subsequent changes in performance through post-error slowing, i.e. increased reaction times on trials after an error (Danielmeier et al., 2015; Kennerley and Wallis, 2009; Ridderinkhof et al., 2004; Ullsperger et al., 2014). dACC activity has been found to predict autonomic arousal, as assessed by pupil diameter, during error processing in a cognitive task (Critchley et al., 2005) and to be associated with peripheral cardiovascular arousal during physical and cognitive exercise (Critchley et al., 2003, 2000). It has also been linked to people's ability to detect their own bodily states. Neuroimaging studies have shown the structure and function of the dACC is related to people's sensitivity and ability to detect their own heartbeats (Critchley et al., 2004). Further studies suggested a role of the ACC in the conscious perception of effort (Naccache et al., 2005; Williamson et al., 2006).

Together, these results suggest that the dACC, insula and DLPFC may monitor internal states of other systems. This is likely to include the monitoring of systems involved in cognitive operations, those processing internal bodily states and also systems monitoring exteroceptive, sensorimotor signals. This would make these regions ideally placed to monitor fluctuations associated with fatigue in circuits that are involved in executing effortful tasks (Müller and Apps, 2019), and therefore gives some further hints about brain areas that might underlie fatigue.

1.4.4 Fatigue in neurological disorders: Parkinson's disease in the spotlight

To better understand the brain mechanisms underlying fatigue and its effects, looking into its manifestation in neurological and psychiatric patients, who often experience heightened and persistent levels of fatigue (Chaudhuri and

Behan, 2004; Cullen et al., 2002; Demyttenaere et al., 2005; Lerdal et al., 2009, 2007; Skapinakis et al., 2003), is of course critical. Notably, disruptions in similar brain systems as the ones outlined in the previous sections have also been proposed to underlie abnormal and persistent forms of fatigue in a variety of neurological and psychiatric conditions. Although, to date, the factors underlying persistent, pathological forms of fatigue have not been fully identified and it remains unclear how closely they are related to the mechanisms underlying state fatigue that fluctuates over exertion and rest, several theoretical frameworks have been developed over the years.

For example, one recent theory derived from work in stroke patients has suggested that fatigued patients show a heightened perception of effort that arises due to the inability of top-down corollary discharge signals to suppress signals from sensorimotor systems (Kuppuswamy, 2017). An alternative account of pathological fatigue has proposed that fatigue may arise in interoceptive systems, through a failure to be able to accurately predict internal bodily states (Stephan et al., 2016). Despite focusing on different systems, both of them suggest that the perception of effort and the experience of fatigue are to some extent subjective and that cognitive, in particular predictive and evaluative processes, may be crucial.

An earlier, prominent account of fatigue in neurological disorders has highlighted that impairments in the basal ganglia, including respective midbrain structures, and connected frontal (and other) areas may lead to increased fatigue and to reduced daily activity, and has linked these impairments to reductions in the efficacy of midbrain and connected dopaminergic systems among other factors (Chaudhuri and Behan, 2004, 2000; see also Dobryakova et al., 2013).

Degeneration of midbrain dopaminergic nuclei are a typical characteristic of Parkinson's disease (PD), a neurodegenerative disorder which comprises motor and non-motor symptoms and in which pathological, persistent fatigue is present in the majority of patients (Alberico et al., 2015; Friedman et al., 2016; Herlofson and Larsen, 2002). Although mechanistic accounts have been limited, some have highlighted that the resulting dopamine deficiency in the brain may be associated with fatigue in these patients (Chaudhuri and Behan, 2004, 2000; Friedman et al., 2007). While it is further unclear which, if any, treatments are effective for reducing fatigue in PD (Elbers et al., 2015; Franssen et al., 2014), dopaminergic medications have been proposed as a potential treatment (Kalia and Lang, 2015; Lou, 2009; Schifitto et al., 2008), yet they are more typically given to ameliorate patients' motor symptoms (Armstrong and Okun, 2020; Kalia and Lang, 2015). In addition, dopamine has also been hypothesised to be able to boost energy levels and thus impact on motivation and fatigue in some other disorders such as in depression (Stahl, 2002).

Aside from its potential role in fatigue, dopaminergic medications in PD have in other studies been associated with modulations of reward sensitivity (Muhammed et al., 2016) as well as with decisions to exert physical effort (Chong et al., 2015; Le Bouc et al., 2016; Le Heron et al., 2018b) and cognitive effort (McGuigan et al., 2019) for rewards. They thereby extend work in monkeys and rodents linking dopamine in the basal ganglia to expected effort costs of an action and to tolerance for effort expenditure (Filla et al., 2018; Pasquereau and Turner, 2013; Salamone et al., 2007; Varazzani et al., 2015) and more traditionally to a sensitivity to expected rewards (Tobler et al., 2005). Although the specific functions of dopamine levels in different brain regions and sub-regions are not fully understood yet, these findings might overall be taken to suggest a potential link between dopamine availability, fatigue and motivation to exert effort for rewards.

1.5 Neural underpinnings of effort-based decisions[3]

Recent theoretical accounts and empirical research have provided an increasingly rich understanding of the cognitive and neural mechanisms underlying people's evaluations of whether it is worth exerting effort, highlighting crucial roles of cortical areas similar to the ones in which activity changes with both cognitive and physical fatigue as well as highlighting a crucial role of the neurotransmitter dopamine (Cools, 2015; Le Heron et al., 2018a; Salamone et al., 2016; Westbrook et al., 2013; Westbrook and Braver, 2016). The most commonly implicated areas in effort-based decision-making are the dACC, the DLPFC (in particular the middle frontal gyri), the AI, as well as the interconnected ventral striatum (VS; in particular the nucleus accumbens [NAc]) and frontal pole (Apps and Ramnani, 2014; Chong et al., 2017; Croxson et al., 2009; Dixon and Christoff, 2014; Kurniawan et al., 2013; Prévost et al., 2010; Salamone et al., 2016; Schmidt et al., 2012; Soutschek et al., 2018; Vassena et al., 2014; Verguts et al., 2015; Winstanley and Floresco, 2016).

Lesions to dACC and VS in rodents reduce the willingness to exert effort in classical T-maze tasks where rodents make choices between a high amount of reward that requires additional effort and a low reward that does not (Rudebeck et

[3] Most parts of this section have been published in the meantime (Müller, T., Apps, M.A.J., 2019, *Neuropsychologia*). Permission to include the material in this thesis has been given.

al., 2006; Salamone et al., 2016; Walton et al., 2006; Winstanley and Floresco, 2016). In non-human primates, the firing rates of single neurons in the DLPFC and ACC respond to how rewarding and how effortful actions will be (Kennerley et al., 2009; Kennerley and Wallis, 2009). Neuroimaging studies in humans have shown that BOLD signals in the AI, dACC, DLPFC and VS areas co-vary with the amount of cognitive and physical effort required (Botvinick et al., 2009; Chong et al., 2017; Schmidt et al., 2012; Shenhav et al., 2017; Vassena et al., 2014).

In more recent investigations, there is evidence that the cortical regions involved in choosing to allocate effort may be related directly to subjective valuations of exerting effort for reward, regardless of the type of effort to be exerted, rather than to the preparation for the execution of effortful acts. Klein-Flügge et al. (2016) found that activity in the dACC was linked to the subjective valuation of choosing to exert physical effort for rewards, specifically to the difference between the subjective values of the chosen and unchosen options, even though effort was only exerted on a small proportion of trials. Chong et al. (2017) also examined how willing people were to choose to exert effort in order to obtain rewards, while the effort was parametrically varied in terms of either cognitive or physical demands. However, participants did not exert the effort inside the MRI scanner. Instead, they were instructed that a proportion of their choices would be chosen at random at the end of the choice task and they would have to exert the effort outside the scanner afterwards. This ensured that activity related to the choices could be examined independently of any potential effects of preparing to exert effort or any potential effects of fatigue. They found that the DLPFC, AI and dACC all signalled the effort-discounted value of rewards, or more precisely the value difference between options, and did so regardless of whether the effort was in the cognitive or physical domain.

Theoretical accounts have also linked these regions to persistence and sustaining motivation throughout a task, in order to reach more temporally extended goals. The dACC in particular has been linked to ascribing value to different courses of action throughout extended sequences of behaviour and to switching to alternative courses of action when the current course of action no longer has sufficient value (Holroyd and McClure, 2015; Holroyd and Yeung, 2012; Kolling et al., 2016a, 2016b; Umemoto et al., 2019). Stimulation of the human dACC further lead to reports of anticipating a challenge and a strong, sustained motivation to overcome it, consistent with the idea of motivating extended behaviours (Parvizi et al., 2013).

Overall, this collection of research shows that activity in partly distinct but also overlapping brain areas has been associated with changes in behaviour likely linked to fatigue and with effort-based decisions (see also **Figure 3**). It suggests that areas which are involved in guiding decisions of whether to exert effort for rewards are also under the influence of the effects of fatigue, and therefore gives a first indication of the neural systems that may underlie the impact of fatigue on the willingness to exert effort. In particular activity in dACC and DLPFC appears to be relevant, while the AI has also been implicated in the processing of action outcomes and in particular of rewards, for example in a recent study on monkeys (Wittmann et al., 2020), in the processing of risks in humans (Burke et al., 2013), in momentary happiness (Rutledge et al., 2014) as well as in interoception and awareness more generally (Craig, 2009) and its precise role in effort-based decision-making and fatigue remains somewhat unclear. Typically, the studies examining effort-based decisions either did not fully dissociate the decision phase from the execution phase or they designed their tasks in a way to specifically investigate the choice phase without having participants perform their chosen efforts whilst undergoing brain imaging. Therefore, how previous exertion impacts on effort-based choices has not been fully unravelled.

1.6 Fatigue and its impact on effort-based decisions: Core brain regions?

The findings reported in the previous sections give some hints about brain areas that might underlie state fatigue and its impact on the motivation to exert effort (**Figure 3**). They suggest that with extended effortful exertion, regardless of whether it is cognitively or physically demanding, declines in performance possibly linked to fatigue are related to changes in activity in several systems. Firstly, cognitive and physical tasks induce changes in areas that are assumed to be directly linked to the performance of the task. For cognitive tasks, this appears to be a diverse set of task-dependent areas, whereas for physical tasks, these changes are primarily in areas involved in sensorimotor control and interoception that are putatively linked to controlling and monitoring the physiological consequences of actions. Secondly, there is a domain-general set of areas that show altered activity across both cognitive and physical tasks. As such, the repeated execution of the cognitive or motor processes necessary for a task and associated changes in systems underlying motor, interoceptive, or cognitive information processing could be expected to contribute to heightened perceptions of effort during exertion and to fatigue (Müller and Apps, 2019).

The connections from these systems to the areas involved in monitoring the internal states of other systems and in evaluating the costs and benefits of exerting effort into behaviours, as outlined in the previous section, presumably lead to their internal states being integrated into the information processed within regions that guide motivated behaviour. In particular, here it is proposed that with increasing levels of fatigue, the weight given to the costs of exerting effort during cost-benefit evaluations is amplified and decisions of whether a behaviour is worth it, e.g. of whether to exert effort into subsequent trials of a task in order to obtain rewarding benefits, will be biased towards rejecting effortful options. As such, fatigue would lead to a drop in the value ascribed to exerting subsequent efforts relative to pursuing alternative courses of action and people would be less motivated to work (Müller and Apps, 2019).

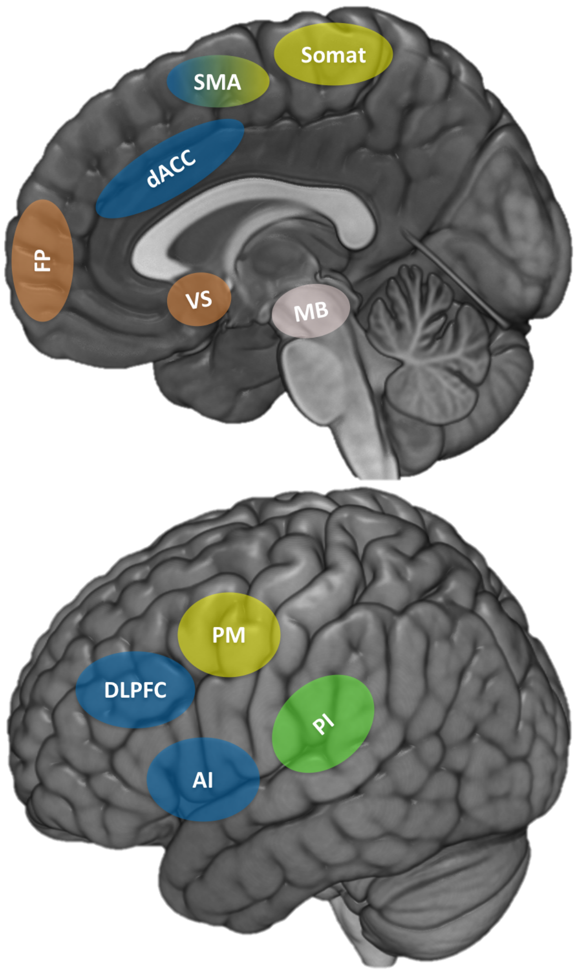

Figure 3. **Schematic display of interconnected regions in the brain in which alterations in neural activity may be associated with fluctuations in fatigue and in the motivation to exert effort for rewards**. Fatigue has commonly been linked to interoceptive and sensorimotor systems, including but not limited to those highlighted in green and yellow respectively on the brain image, as well as to cognitive areas which are rather distributed across the brain. Ventral striatum (VS; in particular nucleus accumbens) and frontal pole (FP) have been implicated in effort-based decision-making. Dorsolateral prefrontal cortex (DLPFC; areas 46 and 9/46), anterior insula (AI; area idg), pre-supplementary motor area (pre-SMA) and dorsal anterior cingulate cortex (dACC; in particular areas 24c'/32' and RCZp/RCZa) have been found to evaluate the costs and benefits of exerting effort as well as to be involved in other related processes, and activity in these regions tends to fluctuate during fatiguing tasks. Dopamine deficiency in the midbrain (MB; encompassing ventral tegmental area and substantia nigra) and connected striatal and frontal regions has been associated with altered effort-based decision-making and potentially with increased fatigue. Premotor cortex (PM), supplementary motor area (SMA) including pre-SMA, somatosensory cortex (Somat), posterior insula (PI). This adapted figure as well as the original version, published in Müller and Apps (2019), have been produced by myself.

1.7 Thesis aims and outline

Theoretical accounts have suggested that the effects of fatigue are closely linked to motivation, arguing that exerting effort can lead to a reduction in the subsequent willingness to exert effort (Boksem and Tops, 2008; Hockey, 2011; Kurzban et al., 2013; Marcora, 2008; Müller and Apps, 2019; Tanaka and Watanabe, 2012), i.e. to *motivational fatigue* (Müller and Apps, 2019). The overlap in activation patterns and the anatomical connections between regions implicated in motivating the exertion of effort and those that have been assumed to signal the effects of fatigue suggests that brain systems that are involved in guiding decisions of whether to exert effort are also under the influence of fatigue.

Yet previous work, typically testing the general population or athletes, has examined fatigue and its impact on motivation and behaviour either over short timescales in the range of seconds (e.g. within a trial) or over longer timescales such as in the range of minutes or hours (e.g. across blocks of a task; over the course of a day; pre versus post exhaustion), has oftentimes assessed fatigue indirectly (e.g. inferred through declines in performance) and has mostly not manipulated important factors systematically such as the amount of effort required and the magnitude of reward on offer. These shortcomings have made it difficult to precisely measure fatigue, its dynamics and its impact on the willingness to exert effort and to distinguish fatigue from other factors such as sleep deprivation, satiety or boredom. On the other hand, levels of fatigue and motivation in patient populations are commonly assessed with self-report questionnaires, which are highly subjective and typically do not systematically capture fluctuations in fatigue and motivation. As a result, to date, we have a poor understanding of the psychological processes, the neural systems and neuromodulators that underpin fatigue. Moreover, it remains unclear how fatigue impacts on the motivation to expend effort for rewards. Therefore, the aim of my thesis is:

To provide a better understanding of the mechanisms in the brain underlying fatigue and its impact on the subsequent willingness to exert effort

In order to precisely measure and quantify how fatigue changes over time and how levels of fatigue impact on the willingness to exert effort, I am using novel computational modelling approaches in combination with new physical effort-based decision-making paradigms and self-report measures. Such computational models are particularly well suited for examining latent variables and processes over time and their implementations in the brain (Corrado and Doya, 2007; Mars et al., 2012). In addition, neural mechanisms are investigated by means of functional Magnetic Resonance Imaging (fMRI) in healthy young people, which allowed specification of neural activity in multiple brain regions simultaneously, and by means of pharmacological manipulation in Parkinson's disease (PD) patients, aimed at examining the role of the neurotransmitter *dopamine* in a sample that typically experiences heightened levels of fatigue. Crucially, the physical tasks which I employed allowed for the systematic manipulation of effort levels, even whilst undergoing fMRI and even in patients with impaired motor function. The results of the seven experiments, briefly outlined below, will therefore not only be informative for theoretical frameworks of state fatigue and of decision-making but will also have implications for the understanding of pathological forms of fatigue and deficits in motivation that are highly prevalent in many psychiatric and neurological conditions, potentially paving the way for new preventive and therapeutic approaches.

In particular, **Chapter 2** aims to examine how the subjective value of exerting effort to obtain rewards changes on a moment-to-moment (trial-by-trial) basis, due to fluctuations in internal states putatively linked to fatigue and to elucidate the respective roles of specific brain regions. For this purpose, an effort-based decision-making paradigm was developed in which participants made a series of choices about whether to accept or reject offers varying in monetary reward and the amount of physical effort required to obtain the reward whilst undergoing fMRI.

Chapter 3 further examines whether variability in effort-based decisions is related to variability in information gathering (focus of attention towards the effort required versus the reward on offer) and subjective sensitivity to effort and fatigue. Here, before making effort-based decisions, participants were required to decide whether they first wanted to see the effort information or whether they first wanted to see the reward information of the offered work option, with information gathering tendencies being linked to self-reported daily demanding physical activity and fatigue.

Chapter 4 presents three experiments investigating how the conscious experience of effort (perceived effort) and the conscious experience of fatigue (perceived fatigue) develop over repeated exertion as a function of effort exerted, rest taken, and rewards obtained. In the first two experiments, a physically fatiguing task in which effort and reward were parametrically varied was employed and trial-by-trial self-report ratings of perceived fatigue (Experiment 1) or perceived effort

(Experiment 2) were collected. In a third experiment, participants were shown the reward that they had collected only after (instead of before) they had exerted force, in order to control for potential effects of reward on motivation and thus force production.

Chapter 5 examines the effect of dopamine levels in the brain on the rates of fatigue build-up and recovery from physically demanding work in PD. PD patients were tested after taking and after withdrawing from their normal dopaminergic medication over two sessions on the paradigm introduced in Experiment 1 of Chapter 4.

Chapter 6 is aimed at further examining the relationship between the effects of repeated exertion on perceived fatigue and on the subsequent willingness to continue to exert effort. For this purpose, I created an online study in which participants made a series of effort-based decisions and indicated their fatigue level on a rating scale after each exertion or rest.

Finally, the thesis will conclude with a general discussion of how the empirical findings from these experiments advance our understanding of fatigue and its impact on voluntary, goal-directed behaviour, in particular on the willingness to exert effort. In addition, I will outline some practical implications of the findings as well as potential avenues for future research.

2 Neurocomputational mechanisms of the impact of fatigue on motivation[4]

2.1 Introduction

Most daily tasks require the exertion of effort over an extended period of time. From a workout at the gym to deciding whether to persist with a task at work, much of our activities require us to keep deciding whether the effort is worth it. People differ widely in how able they are to persist, often attributing failure to sensations of fatigue. Pathological disruptions to the willingness to exert effort are highly prevalent in psychiatric and neurological disorders, and are a hallmark of the clinical symptoms of fatigue and apathy in these conditions (Chaudhuri and Behan, 2004; Husain and Roiser, 2018; Le Heron et al., 2018a; Pessiglione et al., 2018). Recent research has begun to provide a richer understanding of the computational and neural mechanisms underlying how people value, and decide, whether a given amount of effort is "worth it" for a certain magnitude of reward (Apps et al., 2015; Apps and Ramnani, 2014; Chong et al., 2017; Hartmann et al., 2013; Meyniel et al., 2013; Shenhav et al., 2017; Soutschek et al., 2018; Vassena et al., 2014; Westbrook et al., 2019; Westbrook and Braver, 2015). However, implicitly such studies have often assumed that the extent to which rewards are devalued by effort

[4] Most of this chapter has been accepted for publication (Müller, T., Klein-Flügge, M.C., Manohar, S.G., Husain, M.*, Apps, M.A.J.*, in press. Neural and computational mechanisms of momentary fatigue and persistence in effort-based choice. *Nature Communications*). *equal contribution
Author contributions: Dr. Apps, Prof. Husain and I designed the experiment, and I collected the data. Dr. Apps, Dr. Klein-Flügge, Prof. Manohar and I contributed to analysis code and Dr. Apps, Dr. Klein-Flügge and I analysed the data. All of the analyses reported here were conducted by myself. I produced the figures and wrote the initial draft. Dr. Apps, Prof. Husain and I wrote the manuscript.

is consistent over time within people. Yet, motivation is not static (Müller and Apps, 2019). Sometimes even though the objective difficulty of a task remains the same, motivation wanes, and individuals give up or take a break (Iodice et al., 2017b; Lorist et al., 2005; Massar et al., 2018; Meyniel and Pessiglione, 2014; Stoll et al., 2016).

What are the hidden internal states that change how we subjectively value effort over time and prevent us from persisting? Theories suggest that motivation can be characterised by cost-benefit trade-offs, where the value of a reward is subjectively discounted by the effort required to obtain it. Theoretically, we are willing to work when we consider the value of a reward worth the effort we have to exert to obtain it (Kurzban et al., 2013; Müller and Apps, 2019). Although a number of factors can influence such valuations, a crucial influence has been attributed to sensations of fatigue induced by the exertion of effort. It is argued that as fatigue intensifies, it increases the devaluation of rewards by effort, leading to reductions in the willingness to persist with a task, with less rewarding and more effortful acts likely to be avoided (Boksem and Tops, 2008; Hockey, 2011; Marcora, 2009; Müller and Apps, 2019). In addition, time spent resting can have a restorative effect (Massar et al., 2018), reducing fatigue and concomitantly increasing the willingness to exert effort to obtain rewards. Despite these claims being at the cornerstone of theoretical accounts, few studies have directly tested these tenets. Existing research has shown that higher levels of fatigue are related to a reduced willingness to exert effort for rewards (Draper et al., 2018; Massar et al., 2018). But little work has examined the dynamic, moment-to-moment changes in how willing we are to decide that a reward is worth it for the effort (Boksem and Tops, 2008;

Hockey, 2011; Kurzban et al., 2013; Müller and Apps, 2019; Tanaka and Watanabe, 2012).

Moreover, separate lines of evidence suggest that fatigue may be comprised of distinct components that operate on different timescales. There are short-term increases in fatigue during tasks, which can be reduced by short periods of rest (*recoverable fatigue*) (see Meyniel and Pessiglione, 2014). In addition, there are also longer-term changes that occur after extended periods of exertion for which simply resting may not lead to restoration (*unrecoverable fatigue*) (see Blain et al., 2016). As they increase, both components putatively also increase the devaluation of rewards by effort. However, although these components have been examined separately, there has yet to be a formal framework that unifies them and quantifies dynamic changes in fatigue that shift the value people attribute to exerting effort to obtain rewards on a moment-to-moment basis.

Previous neurophysiological and neuroimaging accounts have highlighted a core system in the brain that processes the costs and benefits of engaging in effortful activities. Activity in sub-regions of the supplementary motor area (SMA)/anterior cingulate cortex (ACC), the middle frontal gyri (MFG), frontal pole (FP), and ventral striatum (VS) have been implicated in computing value and motivating the exertion of effort (Apps and Ramnani, 2014; Bonnelle et al., 2016; Botvinick et al., 2009; Chong et al., 2017; Croxson et al., 2009; Klein-Flügge et al., 2016; Kurniawan et al., 2013; Schmidt et al., 2012; Soutschek et al., 2018; Westbrook et al., 2019). Evidence suggests that these regions also change their response with time on task (Iodice et al., 2017b; Müller and Apps, 2019; Stoll et al., 2016). However, it is unclear how this distributed system changes on a moment-to-moment basis, and how that might lead to changes in the value ascribed to exerting effort for reward. Do sub-regions within this network reflect changes in internal states over different timescales, leading to shifts in valuation, i.e. *motivational fatigue*?

Here, it was hypothesised that the brain regions outlined above, that have previously been linked to effort-based decision-making, covary differentially with recoverable fatigue, unrecoverable fatigue, and the momentary value of working (fatigue-weighted value). To test this notion, a novel effort-based decision-making task was designed where participants had to exert physical effort (grip force) to obtain rewards (credits) whilst undergoing functional Magnetic Resonance Imaging (fMRI). On each trial of this task, they chose between a 5 second rest (no effort, low reward [1 credit]) and 5 seconds of work which varied in effort (30-48% of maximum grip strength) and reward (6-10 credits). Using a computational model combining previous cost-benefit valuation models with latent fatigue variables, it was predicted how effort-based decisions would change across the task**.** Using this design, I was then able to identify and dissociate brain regions in which the blood oxygen level dependent (BOLD) signal varied with the hidden variables of recoverable fatigue (RF), unrecoverable fatigue (UF), and fatigue-weighted subjective value (SV) on a trial-by-trial basis at the time of making effort-based decisions.

2.2 Methods

2.2.1 Participants

39 young, right-handed participants with normal or corrected-to-normal vision and no history of neurological or psychiatric illness were recruited through the Oxford Psychology Research participant recruitment scheme and respective online bulletin boards. Written informed consent was obtained from all participants prior to the experiment. The study was approved by the University of Oxford Central University Research Ethics Committee (MSD-IDREC-C1-2014-037). One participant did not fully complete the experiment because of feeling uncomfortable in the MRI scanner and was therefore excluded from the analyses, and a further two participants were excluded due to excessive head motion (more than 6mm of translation). This sample size was selected based on previous fMRI studies in which similar samples evoked responses in hypothesised regions (Blain et al., 2016; Chong et al., 2017). The final sample of 36 participants (16 females) had a mean age of 25.31 years (*SD* = 4.90; range 18-40). Participants were remunerated with £25 for taking part in the study, plus a possible £10 further as a bonus payment. The bonus depended on the credits accrued on all successfully executed trials of the main task, as well as trials executed during the training and pre-task phase. Thus an increase in the bonus was an incentive on every trial.

2.2.2 Apparatus

Stimulus presentation and response collection were implemented using Matlab (MathWorks, Inc., USA) and Psychophysics Toolbox extensions (Brainard, 1997). Grip force was measured using an MRI compatible, handheld dynamometer (TSD121B-MRI; BIOPAC Systems, Inc., USA) with padded "squash" tape to reduce discomfort. Analysis was performed in Matlab 2017b and Statistical Parametric Mapping (SPM12, Wellcome Department of Imaging Neuroscience, University College London, https://www.fil.ion.ucl.ac.uk/spm). Imaging data was collected at the Oxford Centre for Functional Magnetic Resonance Imaging of the Brain (FMRIB) / Wellcome Trust Centre for Integrative Neuroimaging (WIN) using a 3T Siemens Magnetom Prisma MRI scanner with a 32-channel head coil for signal transmission and reception. Choice responses were collected using a 4-button response pad.

2.2.3 Experimental design and procedure

The aim of this experiment was to examine the hidden states that lead to changes in the willingness to exert effort over time and their neural correlates. A physical effort-based decision-making task was developed (**Figure 4**), in which effort was operationalised as the amount of grip force that needed to be exerted for a sum total of 3 seconds in order to obtain reward (credits). The main task of the experiment was performed inside the MRI scanner, but in total the task consisted of four different phases.

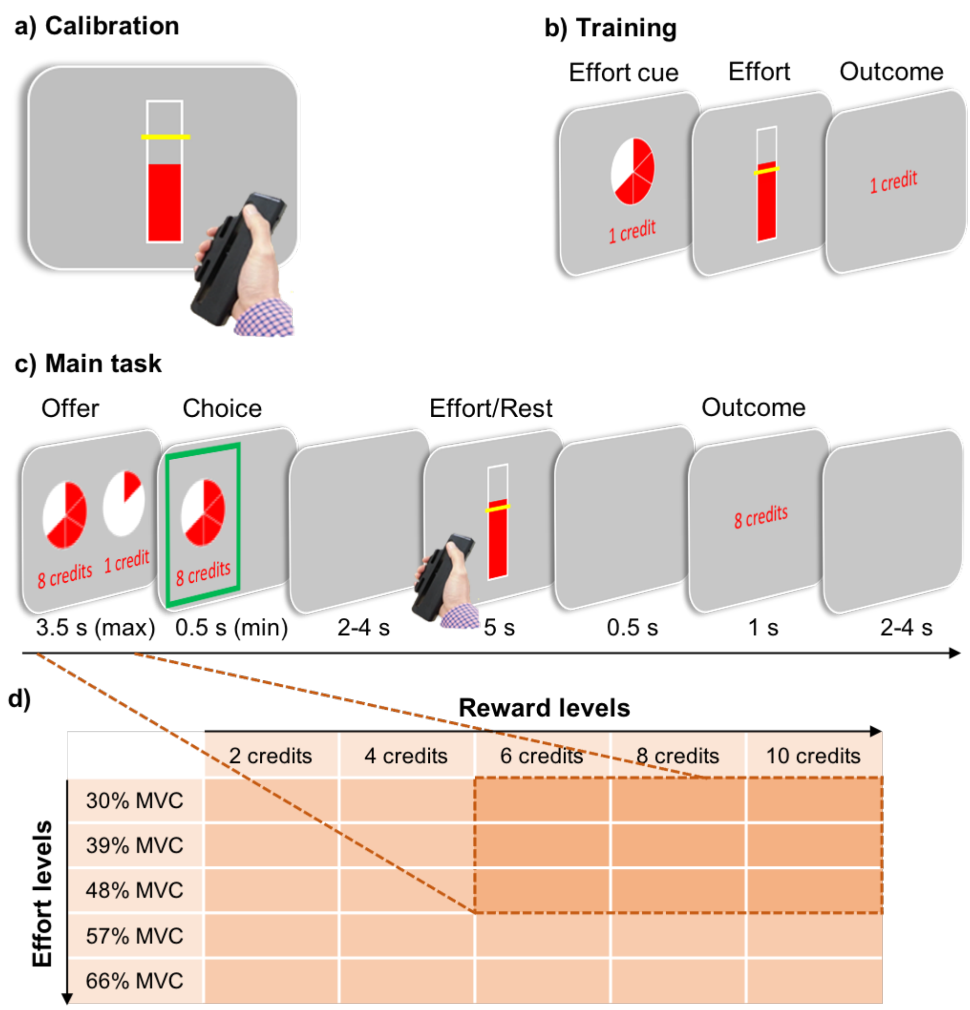

***Figure 4*. Trial structure and experimental design. (a)** Participants were required to squeeze a dynamometer as hard as they could in order to calibrate the effort levels to their individual maximum voluntary contraction (MVC). **(b)** Participants performed a training session to familiarise themselves with how much force was required at each level of effort (0, 30, 39, 48, 57, 66% MVC) and to associate those effort levels with the corresponding pie chart, for which the number of elements indicated the required effort level. **(c)** Participants made a series of choices between a work offer that varied in reward and effort, and a rest offer which never required any force to receive 1 credit. The location (left/right) of the work and rest options was randomised across trials. To obtain the credits chosen, participants had to exert the required force, indicated by a yellow line, for a sum total of 3s out of a 5s window, with a red colouring providing online visual feedback. Unlike in the Main task, in a Pre-task conducted outside the scanner only 10% of randomly selected trials resulted in the subsequent requirement to work if chosen, while in the remaining trials the screen remained blank after the choice period for an average of 12.5s. **(d)** Work offers ranged between 5x5 effort and reward levels in the pre-task and between 3x3 effort and reward levels in the main task (darker orange). All stimuli were presented on a black background.

The *Calibration* phase was aimed at calibrating the levels of effort (grip force) to account for individual differences in grip strength. Therefore, each participant's maximum voluntary contraction (MVC) was measured at the beginning of the experiment by squeezing a hand-held dynamometer on three consecutive trials with their dominant (right) hand. Participants were required to apply as much force as possible on each trial, and they received strong verbal encouragement while squeezing. During each attempt, a bar presented on the screen provided feedback of the force being generated. In the second and third attempts, a benchmark representing 105% and 110% respectively, of the previous best attempt was used to encourage participants to improve on their score. The maximum level of force generated throughout the three attempts was used as the participant's MVC to calculate levels of force required for each participant at each effort level.

In the *Training* phase, participants were able to familiarise themselves with the effort levels used across the experiment and learnt how many segments of a pie chart represented each level of force. Participants practiced reaching each of six effort levels (0, 30, 39, 48, 57, and 66% of each participant's MVC). A successful trial occurred only when the force generated by the participant exceeded the required level for a sum total of at least 3 seconds in a five-second window. Practice of the effort levels was repeated three times, resulting in 18 practice trials in total. Each trial commenced with a pie chart, with the number of red segments indicating the upcoming effort level. During the exertion period, participants were presented with a vertical bar, providing them with real-time feedback on their force and indicating the target effort level by a yellow line superimposed on the bar. When it was a “rest” trial, indicated by one element in the pie chart, the bar was presented for the same amount of time but with the yellow line displayed at the bottom of the bar. To make sure that participants carefully and successfully completed this training, they were awarded one credit for each successful squeeze, but 0 credits for a failure.

In the subsequent *Pre-task*, participants performed 75 trials of an effort-based decision-making task before entering the scanner, aimed at measuring participants’ devaluation of rewards (credits) by effort in a situation where they would not be experiencing higher levels of fatigue. Participants were required to decide whether they find the rewards on offer are worth the required effort by making a series of choices between two alternatives: a rest (baseline) option for a low reward (1 credit), and an effort (work) option for a higher reward. Work options consisted of one of five different effort levels, represented by two to six filled segments in a pie chart (cue) that corresponded to 30, 39, 48, 57, and 66% of each participant’s MVC, and one of five different reward levels (2, 4, 6, 8, 10 credits) as numerically displayed below the pie chart. The rest option was represented by one filled segment in a pie chart and “1 credit” numerically displayed below it. The presentation side (left versus right side of the screen) for work versus rest options was counterbalanced across offers and trials. Effort and reward levels for the work option were varied independently and presented in a pseudorandom order to ensure that each effort/reward combination was distributed evenly across the task. Responses had to be made within 3.5 seconds, using their left hand on a button box. Otherwise, “0 credits – Make your choices faster” was written on the screen for the time that participants would have spent working or resting. If participants chose to work, they were required to exert the chosen force on the dynamometer for at least 3 out of 5 seconds in order to receive the credits associated with the work offer. In this pre-task, only a random 10% of trials actually resulted in the requirement to work if chosen. Otherwise, a blank screen was presented instead of the work or rest screen and the outcome screen for the equivalent duration. Participants were instructed of this before the beginning of the task, but they were not told which of the choices would count and which ones would not, and they were instructed to always make their decisions as if they would have to squeeze if they chose the work option. Furthermore, this part included two breaks, i.e. was split up into three blocks, and participants were free to decide when to continue with the task. Thus, levels of fatigue would not be induced in the pre-task. Following this, participants received feedback on each trial regarding their success or failure. If all the required force was exerted for 3 seconds they would receive all of the credits, if they failed to meet this requirement they would receive 0 credits. The choice period in the following trial was separated from the outcome period in the preceding trial and the successive work/rest period by a uniformly jittered interval of 2 to 4 seconds allowing me to examine activity time-locked to participants' choices.

The *Main task* was then performed inside the MRI scanner and was aimed at measuring how participants' valuations of effort and reward change across time. Participants performed 216 trials in the same pseudorandom sequence of a task similar to the pre-task, that differed in three ways. Firstly, the range of work offers was lowered to include only those of high value, the three lower effort levels (30, 39, 48% MVC) and the three higher reward levels (6, 8, 10 credits). This ensured that if participants chose to rest, they were doing so for options that they would choose to work for in the pre-task. This would indicate a shift in the value ascribed to working, which was indeed the case in the behavioural data. Secondly, in the main task every choice counted. Thus, every choice to work resulted in the requirement to exert the required level of effort to obtain the offered reward. Thirdly, there were no breaks included. If participants wanted to take a rest, they had to choose to do so. The duration of all trials (except for jittering) was the same regardless of choices to rest or work, and across the pre and main task. This ensured that participants' choices and associated neural correlates were not due to temporal discounting (Frost and McNaughton, 2017; Kable and Glimcher, 2007; Pine et al., 2009). Participants were very successful across the whole experiment at reaching the required force levels, successfully obtaining credits on $M > 96.8\%$ ($SD < 4.6$) of the respective trials, suggesting that participants' choices were unlikely confounded by outcome uncertainty. The effort levels used in this experiment were chosen as they have been shown not to cause significant build-up of lactate and muscle pain, and the stopping of exertion is driven more by the perception of effort and not pain (Marcora, 2009; Staiano et al., 2018). This ensured that the results are unlikely to be due to muscle pain, which can be incurred at higher levels of grip force. In addition, prior to the main task and at the end of the experiment participants were required to rate between 0 (*not at all*) and 10 (*extremely*) their level of "tiredness". One participant was excluded from analyses of these ratings as data was not appropriately captured.

2.2.4 Behavioural analysis

To determine whether the willingness to exert effort changes as a function of effort, reward, and the history of effortful exertion, logistic regressions (using Matlab's *glmfit* function) on choices, with offered effort and reward levels of the work option as predictor variables were conducted for each participant. To analyse choices in the main task, cumulative effort (the sum total of effort exerted during the task prior to the current trial), as well as interactions of effort and reward levels (z-scored) with cumulative effort were added as additional predictor variables. All regressors were z-scored for each participant, i.e. mean centred and divided by the standard deviation. Regression models were fitted to each participant's choice data, and statistical inference was made at the group level by comparing t-scores across participants against zero. Beta values for each participant's regression coefficients were normalised to t-statistics as $\beta/SE(\beta)$ in order to compensate for the possibility of poor estimates of βs in participants with low levels of variance. Because the t-scores were not normally distributed, they were tested for significant deviation from zero using two-tailed non-parametric Wilcoxon signed-rank tests. Confidence intervals (CIs) for Wilcoxon tests are based on the Hodges-Lehmann estimate (median).

2.2.5 Computational modelling

2.2.5.1 Modelling subjective value

Theoretical accounts and existing empirical data have suggested, but largely not formalised, the notion that fatigue can influence motivation on multiple timeframes. Here, a computational model of fatigue was developed and, based on theoretical accounts, was integrated into a parabolic effort-discounting model to explain how effort-based decisions change over-time due to hidden recoverable and unrecoverable components. This model could be fitted separately to each participant's behaviour. In line with previous work on how rewards are parabolically discounted by physical effort (Chong et al., 2017; Hartmann et al., 2013; Lockwood et al., 2017), I fitted a simple discounting model to the pre-task choice behaviour. The model assumed that the value of the work offer depends on how rewarding it is, how much effort is required and how participants subjectively weigh these to guide their choices to work or rest. That is:

$$SV_{(t)} = R_{(t)} - (k * E_{(t)}^{2}) \tag{1}$$

where $SV_{(t)}$ represents the subjective value of the work option on trial t, and k the subject-specific discount parameter, scaling the devaluation of a reward (R, reward level 2, 3, 4, 5, or 6) by the effort (E, effort level 2, 3, 4, 5, or 6) required to obtain the reward. The higher an individual's k parameter, the steeper an individual's discount function, i.e. the more this individual's valuation of rewards is discounted by the effort required to obtain the rewards. To fit the model to the data, I used a softmax function, which estimates the probability $P_{(i,t)}$ that a participant will choose the work option i that has a subjective value SV over the rest option that has a value of 1 (one credit, no effort), defined as:

$$P_{(i,t)} = \frac{e^{SV_{(i,t)}*\beta}}{e^{1*\beta} + e^{SV_{(i,t)}*\beta}} \tag{2}$$

Since the baseline SV was fixed at 1 (one credit, no effort), when the baseline was chosen $P_{(i,t)}$ was calculated according to $P_{(i,t)}$ = 1-$P_{(i,t)}$. Maximum likelihood estimation, using the *fminsearch* function in Matlab, was used to minimise the difference between each participant's actual choices and the model estimates for each trial, i.e. to minimise the negative log-likelihood. This fitting procedure was used to fit choices in both the pre-task and main task.

The estimates of the discounting parameter k and the level of stochasticity in the choices (β) were restricted not to go below 0.0276 (in which case even the combinations of lowest reward and highest effort are always accepted) and 0, respectively. The model was fitted 50 times using different random starting values (using *rand*) to ensure that the optimisation function had not settled on a local minimum. By fitting this model to the pre-task, I was able to quantify a participant's typical willingness to exert effort for reward, and the noisiness in such choices, during a task that would not evoke fatigue. The k and β parameters obtained for each participant in the pre-task were used as fixed parameters in the models fitted to choices in the main task.

2.2.5.2 Modelling fatigue-weighted subjective value (full model)

Based on theoretical accounts it was hypothesised that fatigue would increase with exerted effort, would be partially recoverable and decrease with time spent resting, but would also have a gradually increasing unrecoverable component which did not recover with rest (Blain et al., 2016; Hockey, 2011; Meyniel et al., 2013; Müller and Apps, 2019). This fatigue impacts value, such that when the levels of fatigue were higher, participants would be less willing to work. Thus, a model was developed including recoverable and unrecoverable components of fatigue, fluctuating over the experiment, that were integrated into the value-based model in Equation 1:

$$SV_{(t)} = R_{(t)} - ((RF_{(t)} + UF_{(t)}) * k * E^2_{(t)}) \quad (3)$$

In this full model, rewards (R) are devalued by effort (E), subjectively weighted by the discount parameter k from the pre-task. In addition, this discounting effect fluctuates trial-to-trial by levels of recoverable (RF) and unrecoverable (UF) fatigue. RF subjectively increases if a person exerts effort, i.e. accepts the work offer (Equation 4), with the work parameter α scaling the amount that effort increases RF, and subjectively recovers by time resting (T), as captured by the rest parameter δ (Equation 5). UF subjectively accumulates depending on the effort exerted across the whole task, scaled by parameter θ, and is not restored by resting (Equation 6):

$$RF_{(t)} = RF_{(t-1)} + (\alpha * E_{(t-1)}) \quad (4)$$

$$RF_{(t)} = RF_{(t-1)} - (\delta * T_{(t-1)}) \quad (5)$$

$$UF_{(t)} = UF_{(t-1)} + (\theta * E_{(t-1)}) \quad (6)$$

The subjective value SV and the fatigue levels RF and UF were updated for each trial t (initial RF and UF = 0.5) and fed into the softmax (Equation 2) as above, to estimate P in each trial. Based on theoretical considerations, only parameter values >= 0 and RF estimates >= initial RF were allowed. Missed trials, which were very rare (*M* = 0.57% of all trials, *SD* = 1.71), were treated as rest trials. To maximise the chances of finding global rather than local minima, parameter estimation for the full model and for all alternative models (see below) was repeated over a grid of initialisation values, with 12 initialisations (ranging from 0 to 1.1) per parameter. The optimal set of parameters for each model was used for model comparison and for further analyses.

2.2.5.3 Model comparison

To verify whether the three parameters used to quantify the effects of fatigue were necessary, alternative models were also fitted to participants' choices in the main task. These models either contained no effect of fatigue (two null models), an effect of UF only (i.e. θ being fitted) or an effect of RF only (i.e. α and δ being fitted). The two null models predicted no effect of fatigue in the main task: One used the original pre-task discounting parameter (k) and thus assumed that the willingness to exert effort stayed the same across the whole experiment, and in a second a new discounting parameter (γ) was calculated across all trials in the main task thus assuming a fixed change in the willingness to work between the pre and main tasks. In addition, two further mathematically plausible but theoretically unlikely models were included which used only one parameter to scale the effect of effort and rest on recoverable fatigue (i.e. only α being fitted across both work and rest trials). In one of these models this fatigue was only comprised by this one parameter RF, while in a second model, fatigue comprised UF plus the one parameter RF. In the models including a fatigue term, initial RF and UF values were defined such that the initial total fatigue was always equal to 1.

In order to investigate the models' relative ability to predict the behavioural data, model fits were compared using the Akaike Information Criterion (AIC; Akaike, 1974) and Bayesian Information Criterion (BIC; Schwarz, 1978) with lower values indicating better fit. Model fit to a given data pattern can be improved by simply adding additional parameters, and thereby models with more parameters may be overfitted. AIC and BIC punish models with more free parameters and favour the most parsimonious solutions by adding a penalty term to the log-likelihood (LL) which depends on the number of parameters (d) and in the case of BIC also on the number of observations, i.e. the number of trials (n):

$$AIC = -2 * LL + 2 * d \tag{7}$$

$$BIC = -2 * LL + d * \ln(n) \tag{8}$$

2.2.6 Functional imaging and analysis

2.2.6.1 fMRI scan acquisition

For anatomical localisation, a high-resolution, three-dimensional structural T1-weighted image was acquired using a magnetization-prepared rapid gradient echo (MPRAGE) sequence with 192 slices [slice thickness = 1mm, repetition time

(TR) = 1900ms, echo time (TE) = 3.97ms, flip angle = 8°, field of view = 192mm × 192mm, voxel size = 1×1×1 mm]. A total of 2355 whole-brain functional T2*-weighted echo planar images (EPIs) were acquired with a tilted-plane sequence with a pitch of 30°, in order to reduce potential image distortions and signal losses caused by susceptibility gradients near air/tissue interfaces (Deichmann et al., 2003), using multiband factor acceleration interleaved slice acquisition [72 slices, slice thickness = 2mm, TR = 1570ms, TE = 30ms, flip angle = 70°, field of view = 216mm × 216mm, voxel size = 2×2×2 mm]. Subsequent to the functional sequence, a gradient echo field map sequence was used to collect phase and magnitude maps (TE_1 = 4.92ms, TE_2 = 7.38ms) in order to correct for geometric distortions caused by magnetic field inhomogeneities.

2.2.6.2 Image preprocessing

Imaging data were preprocessed and analysed using SPM12. First, to correct for head motion within participants, each EPI in a participant's time-series was realigned to the mean image using a least squares approach and a six parameter, rigid body spatial transformation (Friston et al., 1996) with B-spline interpolation. Additionally, the acquired field maps were used to estimate the amount of non-linear distortion from magnetic field inhomogeneities for each functional image and to correct for the movement-by-distortion interactions (Andersson et al., 2001; Hutton et al., 2002). Following this, the mean of the realigned and unwarped functional images was coregistered to each participant's own structural image, based on Collignon and colleagues (Collignon et al., 1995), to ensure better anatomical localisation and greater precision in spatial normalisation. Next, the coregistered structural image was segmented into tissue probability maps based on standard stereotaxic space (Montreal Neurological Institute, MNI), bias-corrected and normalised to the MNI template (Ashburner and Friston, 2005). The same normalisation parameters were used to convert the realigned and unwarped functional images into standard space. Functional images were then resampled to a voxel size of 3×3×3 mm and spatially smoothed using an 8mm full-width-half-maximum Gaussian kernel in order to improve the signal-to-noise ratio.

2.2.6.3 First-level statistical analysis

First level whole-brain statistical analyses were performed using general linear models. To examine whether BOLD activity in any voxel parametrically varied with the trial-by-trial estimates of SV, RF and UF from the winning computational model (full model) during decision-making, the averaged and z-scored trial-by-trial estimates for SV, RF, and UF were used as parametric modulators for the offer cue event-related regressor, i.e. the onset of the options screen. To improve overall model fit and account for potential confounds, the design matrix included the following additional regressors which were not analysed: Four regressors that modelled the onset of the work/rest screen and the onset of the outcome screen, both separately for work trials and rest trials, as well as a regressor that included all events onsets from trials with a missed response.

Regressors were modelled with a stick (delta) function with 0 seconds duration, convolved with a canonical hemodynamic response function (HRF). For the parametric modulators, a 1st order modulation was selected, i.e. it was assumed that the stick function heights will change linearly over different values of each parametric modulator. Parametric modulators were not orthogonalised with respect to each other. To ensure that the model could be estimated and that respective inferences could be made, the regressors of interest were checked for rank deficiency and statistical independence. Correlations between parametric regressors were all below 0.4 (r = -0.08 between RF and UF; r = -0.09 between RF and SV; r = -0.36 between UF and SV). The six rigid body motion parameters estimated during the realignment step (three translations and three rotations) were added as separate regressors that were not convolved with the HRF to control for nuisance effects resulting from head motion. The high-pass filter cut-off was set to 128 seconds in order to remove low-frequency noise. Regression coefficients were estimated using a restricted maximum likelihood algorithm, using an autoregressive AR(1) model to account for autocorrelations intrinsic to the fMRI time series. Contrasts for each of the three parametric modulators as well as contrasts between them were conducted to identify regions in which the BOLD signal covaried with each regressor independently and in comparison to each other.

In addition, I ran a control analysis in which I added an index of trial-by-trial decision difficulty as a parametric modulator to the design matrix, time-locked to the onset of the offer cue. Decision difficulty for each participant was calculated as $-|P-0.5|$, with P representing the choice probabilities derived from the softmax function from the full model. That is, more difficult decisions should be reflected as probabilities closer to 0.5 (or difficulty = 0), while easier decisions should be reflected as probabilities closer to 0 or 1 (difficulty < 0). Trial-by-trial estimates were then averaged across participants and z-scored. Although this approach is limited by averaging across participants, it ensures that variance is scaled similarly across participants.

2.2.6.4 Second-level statistical analysis

In order to be able to make inferences about the sample population, a random effects second-level statistical analysis was conducted. Therefore, the contrast images from the first level were analysed using one-sample t-tests at each voxel for each contrast of interest. T-contrasts were then applied to identify areas in which activity varied statistically with the parametric modulators. To correct for multiple comparisons, I used a statistical threshold of $p < .05$ with voxel-level family-wise error (FWE) correction across the entire brain volume. Because previous studies have emphasised the importance of the VS and the dACC/pre-SMA region in processing effort-based decisions, and in order to be able to specifically localise activity to anatomically and functionally distinct regions, these areas were also probed using a priori regions of interest. Therefore, t-contrasts were conducted at the whole-brain level at an uncorrected statistical threshold of $p < .001$, and then a FWE small volume correction was applied using a combined mask taken from appropriate atlases (bilateral VS: from Harvard-Oxford Atlas; bilateral dACC and pre-SMA: areas RCZa, RCZp and pre-SMA defined through resting-state parcellations of the frontal cortex by Neubert and colleagues (Neubert et al., 2015)). By combining these masks together a more conservative statistical threshold than in individual ROI analyses was provided, balancing possible false negatives that can occur with whole-brain correction.

Additionally, to examine whether activity was modulated by how strongly a participant's choices were affected by RF and UF, each participant's UF parameter, RF work parameter and RF rest parameter from the full model were used as a covariate for the respective UF and RF t-contrasts in separate second-level group analyses. To avoid double-dipping when correlating parameters with voxels which are already known to show a significant result in a non-independent analysis, these analyses were performed by examining whether any voxels showed a significant effect within the ROI masks. Such an approach does have the limitation that the significance between correlations cannot be determined formally. For these analyses, one participant was excluded who had excessively high RF work and rest parameters.

2.3 Results

The aim of this study was to examine how the value attributed to exerting effort to obtain rewards changes on a moment-to-moment basis, due to fluctuations in internal states putatively linked to fatigue. An effort-based decision-making task was designed in which participants would choose between 5 seconds of work or 5 seconds of rest whilst undergoing fMRI (**Figure 4**). Rest required no exertion, but only resulted in accruing a small reward (1 credit). The work offer varied on every trial in both reward magnitude (6, 8, 10 credits), as well as the amount of physical effort (grip force) required to obtain it. These effort levels were calibrated to participants' own maximum grip strength (30, 39, 48% of maximum voluntary contraction [MVC]). Participants had to exert force at the required level for a total of 3 seconds out of the five-second window in order to receive the reward. Failure to do so resulted in 0 credits. Although these effort levels were demanding, they were easily achievable, and participants were successful at executing the required levels of force on over $M > 96.8\%$ ($SD < 4.6$) of trials at all levels of grip force. In addition, participants were required to rate their level of "tiredness" – a more commonly used synonym of fatigue – between 0 and 10 before the main task, and then again after completion of the experiment. Although participants could freely choose to rest, and thus prevent a significant build-up of fatigue, a repeated measures t-test revealed that ratings of fatigue were higher at the end of the experiment than at the beginning ($t(34) = 4.27$, two-tailed $p < .001$, Cohen's $d = 0.72$, 95% CI = [0.54, 1.52]; **Figure 5**).

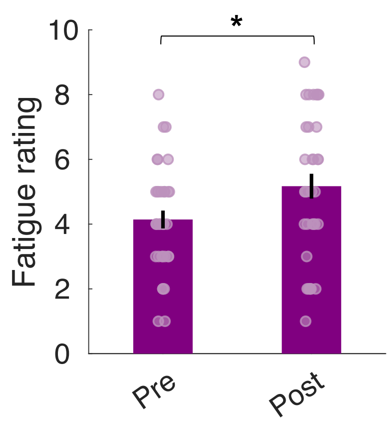

***Figure 5.* Fatigue ratings taken before and after the main task**. Fatigue was higher after the main task than before. The asterisk shows a significant effect ($p < .001$). Each dot represents one subject and error bars reflect SEM.

2.3.1 Effort discounting and persistence depend on the history of exertion

I hypothesised that people's willingness to exert effort for reward would change across trials. More specifically, the computational model built around theories of fatigue and motivation suggests that exerting effort increases levels of fatigue, and when fatigue is higher, the same levels of effort and reward would have a reduced value compared to when fatigue is low. Such an account would predict that (i) participants would be more likely to work in situations where fatigue is low and (ii) people would shift their valuations, such that while higher effort / lower reward offers would be worth working for at some times, they would be avoided in favour of a rest at other times.

To test the first of these predictions I compared choices in the main part of the experiment, where every choice of work resulted in the requirement to exert force for reward, with a pre-task in which only a random 10% of trials resulted in the requirement to exert force. The pre-task also contained a wider range of offers, including options that were lower in reward (*2, 4,* 6, 8, 10 credits), but higher in effort to ensure the full range of variability in people's tendency to discount rewards by effort could be captured (30, 39, 48, *57, 66*% MVC). This pre-task therefore allowed me to measure people's tendency to discount rewards by effort in a task where little fatigue would be accrued. First, I wanted to show that in this pre-task, participants were discounting rewards by effort. A logistic regression (with a Wilcoxon test across participants) on choices to work or rest showed evidence of this, with participants more likely to choose work at higher rewards (Z = 4.43, $p < .001$, 95% CI = [1.15, 2.17]), but less likely to work at higher efforts (Z = -5.11, $p < .001$, 95% CI = [-2.55, -1.35]). However, despite showing effort-discounting effects, participants chose to work on almost all of the trials ($M >= 95.4\%$) for each combination of the higher reward (6-10 credits) and lower effort levels (30-48% MVC) that were included in the main task (**Figure 6**). Thus, when little fatigue could accumulate, participants valued these offers consistently higher than the value of rest and chose to work.

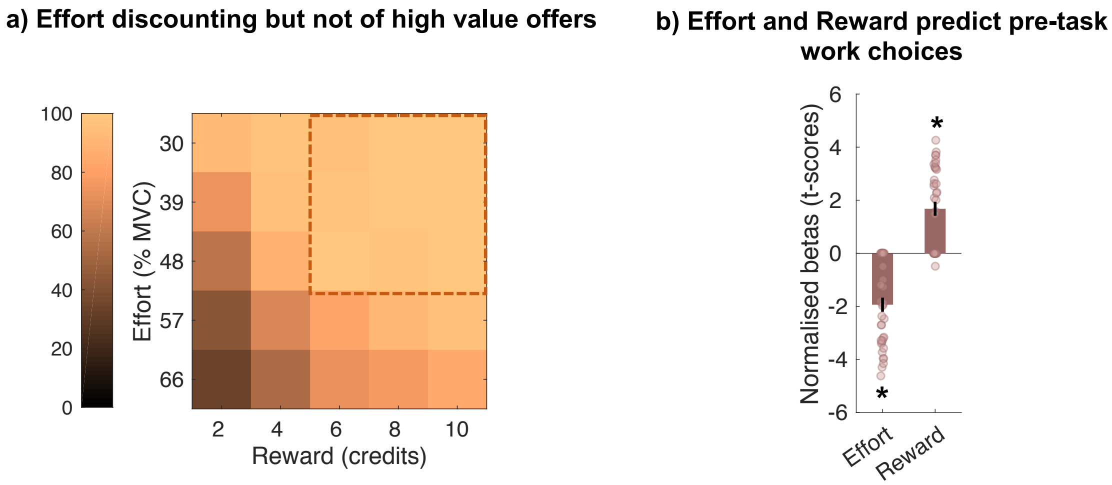

***Figure 6*. Effects of effort and reward on choices to work or rest in the pre-task**. **(a)** Mean proportion of choices to accept the work offer as a function of effort and reward. Participants were more likely to choose to work at higher reward and lower effort. The “high value” work options (inside the dotted line) were almost always chosen as worth working for. **(b)** Logistic regression on the pre-task choice data shows significant positive effects of reward and negative effects of effort on choices to work. The asterisks show significant t-scores ($p < .001$). Each dot represents one subject and error bars reflect SEM.

The second claim that would be predicted by the model is that the value of exerting effort for rewards declines as fatigue accumulates, i.e. participants would shift the value they ascribed to work offers across the main task. To test this, I performed a logistic regression on choices to work or rest (with a Wilcoxon test across participants), using effort, reward (offered on each trial), cumulative effort (sum total of effort exerted from all previous trials) and respective interactions as predictors (**Figure 7d**). Consistent with a dynamic change in the value of working, there was a significant interaction between effort and cumulative effort, as well as main effects of effort, reward and cumulative effort (cumulative effort × effort: $Z = -4.19$, $p < .001$, 95% CI = [-1.39, -0.47]; effort: -4.35, $p < .001$, 95% CI = [-1.83, -0.96]; reward: $Z = 3.96$, $p < .001$, 95% CI = [0.69, 1.71]; cumulative effort: $Z = -3.83$, $p < .001$, 95% CI = [-2.45, -0.84]). The three-way ($Z = -0.27$, $p = .79$, 95% CI = [-0.25, 0.37]) and the cumulative effort × reward interactions ($Z = 1.40$, $p = .16$, 95% CI = [-0.06, 0.42]) were not significant. Importantly, offers that were considered as higher in value and were chosen to work for at a high proportion in the pre-task, became gradually less and less likely to be selected across trials in the main task (**Figure 7**).

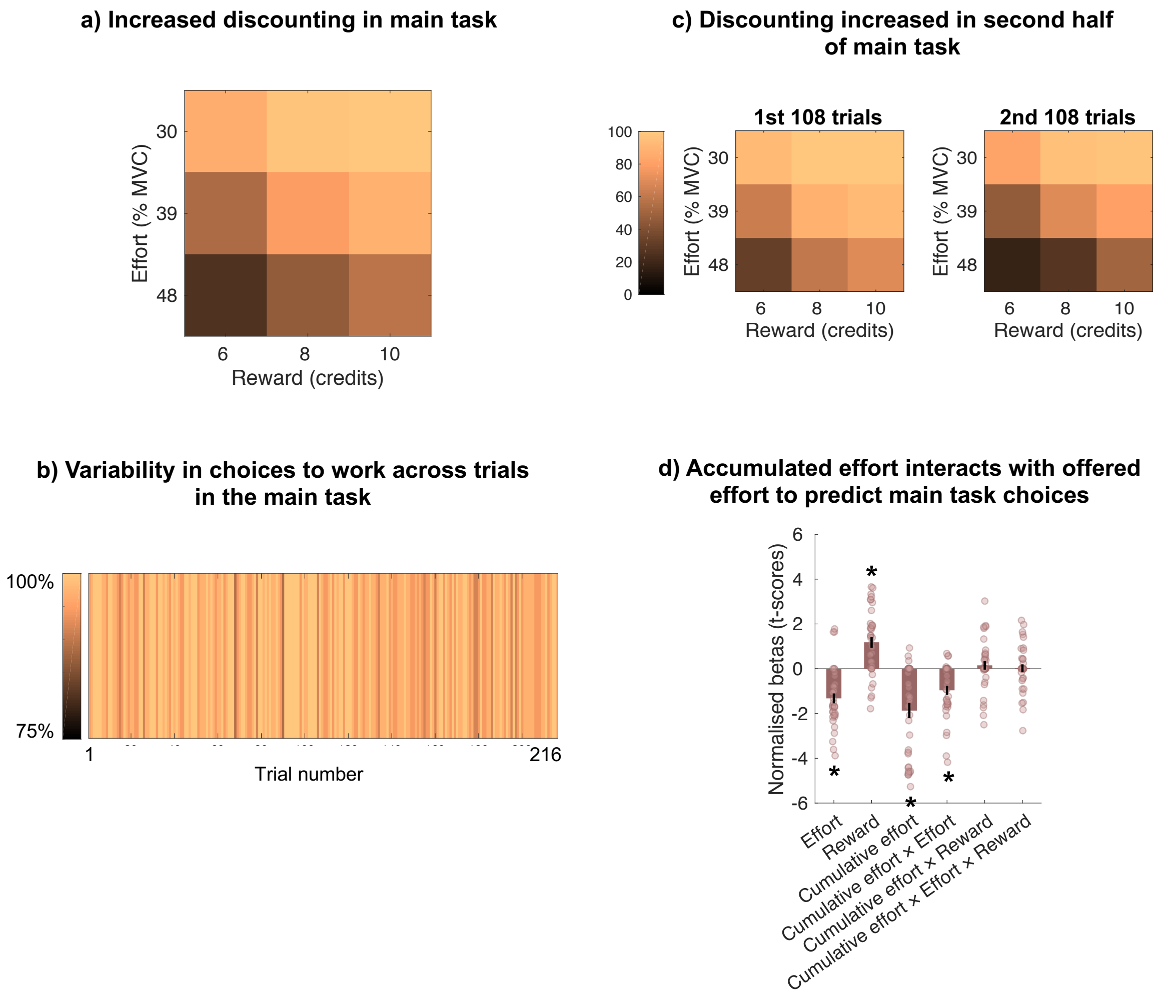

Figure 7. **The shifting of subjective value of effort and reward**. **(a)** Mean proportion of choices to work in the main task, where all choices resulted in subsequent work or rest. Some of the "high value" options previously worth working for are now sometimes avoided. The lowest value of the higher value options (48% effort, 6 credits) is often avoided in favour of a rest in the main task. **(b)** Percentage of participants who accepted the work offer, illustrated separately for each trial in the main task. Values reflect the consistency with which trials were accepted or rejected across the experiment. This shows considerable variability in choices, but high levels of choices to "work" in early trials, rather than late. **(c)** Mean proportion of accepting the work offers in first and second half of the main task. Gradually increasing effort-discounting reflects a shift in valuation of previously high valued offers across time in the main task. **(d)** Logistic regression predicting choices to work or rest in the main task. The effort level in the current trial's work offer interacts with the sum total of effort accumulated up to that trial (cumulative effort) to predict choice. The asterisks show significant t-scores ($p < .001$). Each dot represents one subject and error bars reflect SEM.

Notably, effort and reward still had strong, significant effects when examining only the last quarter of trials (effort: $Z = -5.232$; $p < .001$, 95% CI = [-1.916, -1.420]; reward: $Z = 4.305$; $p < .001$, 95% CI = [0.714, 1.548]), and participants were still choosing to work on almost 100% of trials for the highest reward and lowest effort in the last 27 trials of the main task (**Figure 8**). Such findings are indicative of participants changing their subjective evaluation of working across trials, with accumulated efforts increasing the discounting effect of effort and reducing the value of working across the experiment, and are inconsistent with boredom or other factors potentially leading to generally more noisy or random behaviour in this task.

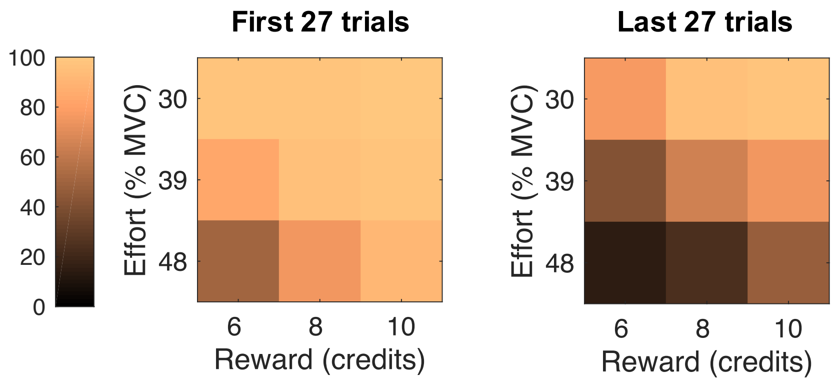

Figure 8. **Shift in choices away from higher effort, lower reward options in last 27 trials compared to first 27 trials in the main task**. The shift in the mean proportion of choices to work does not occur for the lowest effort highest reward offer, consistent with a shift in valuation instead of more random behaviour.

2.3.2 Two fatigue states impact the subjective value of work

To more precisely quantify changes in valuation of effort across the task, a novel computational model of fatigue and its effect on effort-related motivation was developed (**Figure 7**; **Figure 9**). I hypothesised that fatigue has several components that impact on the willingness to exert effort, each of which operates on a different timescale. It was predicted that the value of working fluctuates on a short-term basis due to a build-up of (recoverable) fatigue after exerting effort that is recovered by rest (Meyniel and Pessiglione, 2014). A separate line of evidence suggests that demanding tasks also cause (unrecoverable) "executive" fatigue that cannot be easily restored just by taking some time resting (Blain et al., 2016). Here, a computational model of how these two sources of fatigue would fluctuate trial-to-trial during the task was formalised (**Figure 9**; see Methods). This model contained three free parameters estimated on choices to work or rest in the main task. One parameter (α) scaled the amount that recoverable fatigue increased by the exertion of effort, with a second (δ) scaling the amount that recoverable fatigue was reduced by time spent resting. The third parameter scaled the amount that unrecoverable fatigue increased by exerting effort (θ). The fluctuating recoverable, and gradually increasing unrecoverable, fatigue values were integrated into a parabolic effort-discounting model (Chong et al., 2017; Hartmann et al., 2013; Lockwood et al., 2017), in which rewards were devalued more by effort as levels of the unrecoverable and recoverable fatigue increased. To account for individual differences in people's effort-discounting when participants were not fatigued, I also included a free parameter (k) which scaled how much participants devalued rewards by effort, fitted to choices in the pre-task.

To test whether shifts in people's valuations of effort across the main task were related to hidden recoverable and unrecoverable fatigue states, and whether three parameters were necessary to explain changes in the willingness to work, I performed model comparison. The results showed that the full model (Model 5) fitted better to participants' decisions to work in the main task than six alternative models in which fewer parameters scaled or removed the unrecoverable and recoverable components (**Figure 9**). Findings were comparable when using BIC or AIC suggesting that extra parameters in the full model increased explanatory power.

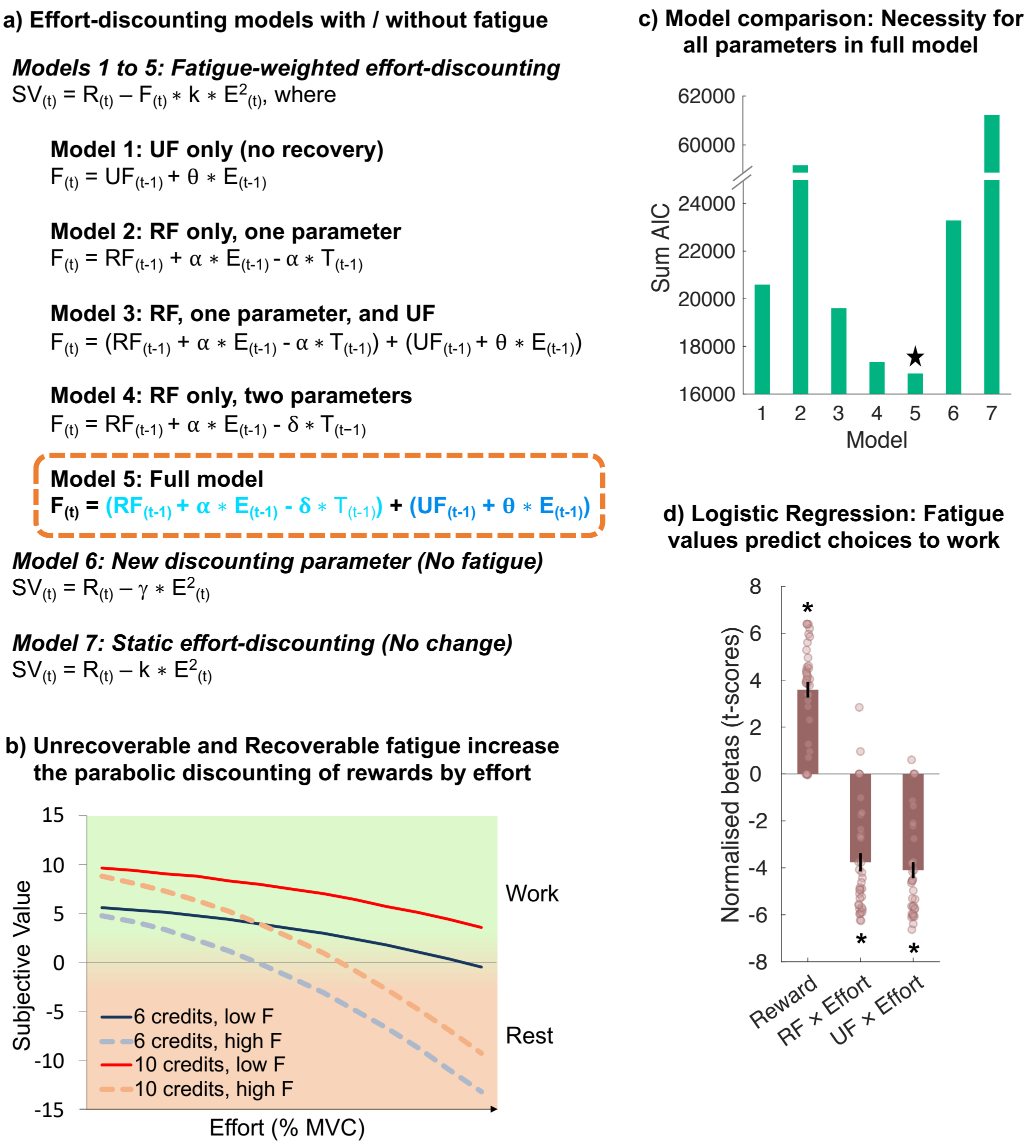

Figure 9. **Modelling the fatigue-weighted subjective value. (a)** List of models compared. All models assume that rewards (R) increase subjective value (SV), effort (E) decreases it, and people discount the rewards by effort idiosyncratically. Models 6 and 7 assume that motivation remains static across the trials of the main task, either with a new discounting parameter (Model 6) or with the same discounting parameter *k* as fitted to the pre-task (Model 7). Models 1 to 5 capture trial-by-trial changes in effort-discounting due to fatigue (F). The full model assumes that exerting effort increases recoverable fatigue (RF), but time (T) spent resting decreases it. Unrecoverable fatigue (UF) also increases through exerted efforts but never declines here. **(b)** Schematic representation for how F affects value and choices to work or rest. **(c)** Model comparison results. The star indicates the winning model. **(d)** Model-estimated RF and UF from the winning model interacted with effort to predict choice behaviour in a logistic regression. The asterisks show significant t-scores ($p < .001$). Each dot represents one subject and error bars reflect SEM.

In addition, given that there was some variability in choice behaviour between participants (**Figure 10**), I calculated exceedance probabilities (Stephan et al., 2009) on the (negative) AIC values for each model in order to test whether the full model was indeed the most likely in the population. Analyses revealed that the full model had the highest probability of being the most frequently best fitting model to participants' choice data (**Figure 10b**). This would suggest that participants made decisions to work based on a fatigue-weighted value, where fatigue depended on recoverable and unrecoverable states.

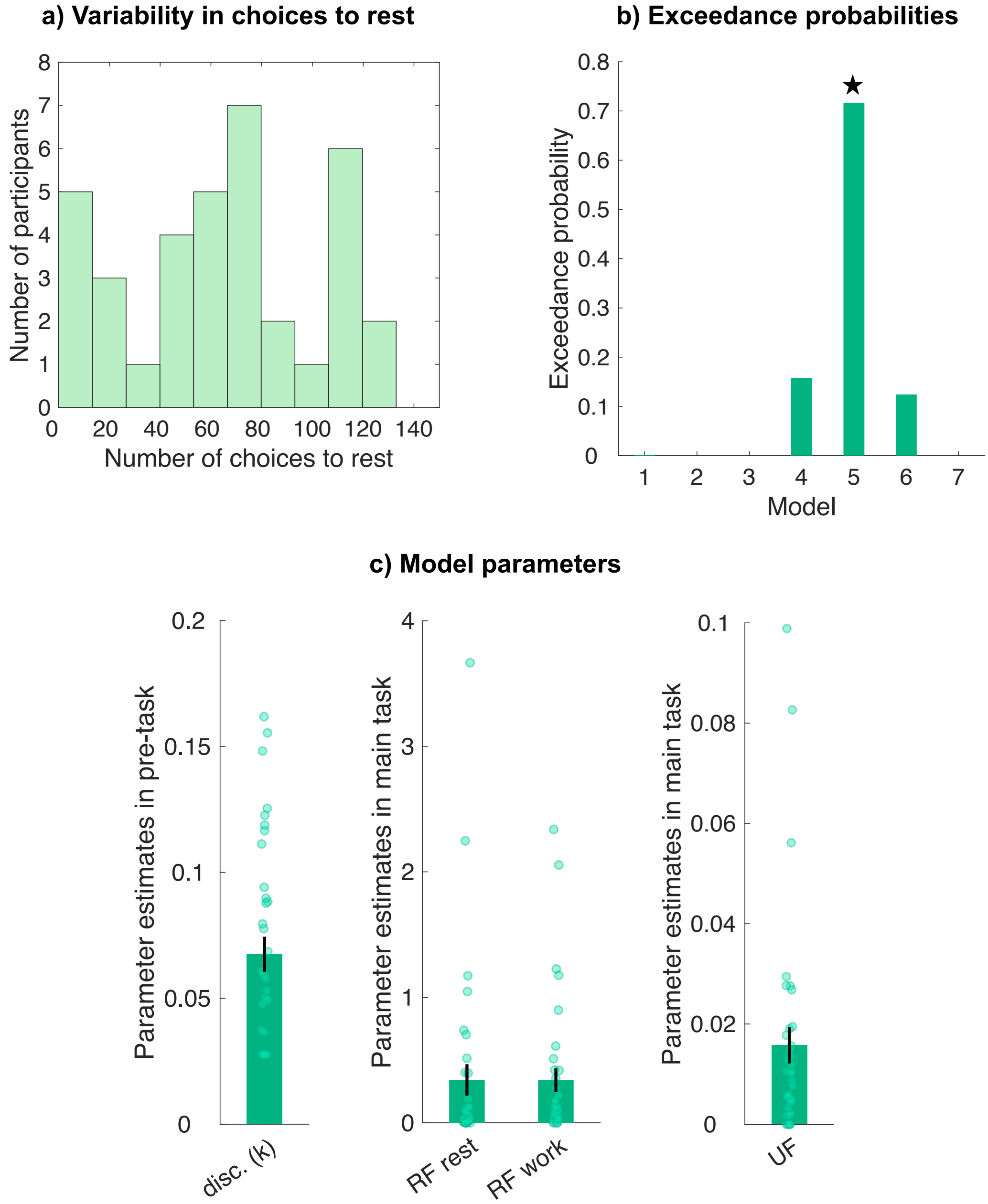

Figure 10. **Variability in choice behaviour. (a)** Histogram of proportion of trials on which participants made choices to "rest" out of 216 trials, showing variability in choices both within and between many participants. **(b)** Exceedance probabilities for the models fitted to the choice data. The y-axis reflects the probability of being the most frequently observed model in the population. The full model (5) is the most likely best fitting model in the population. **(c)** Model parameters for each participant (green dot) and average across participants for the discounting parameter fitted to the pre-task (left), the two recoverable parameters (middle) and the unrecoverable parameter (right). One participant's RF parameters are not included for display purposes due to high values. Error bars reflect SEM.

To test that this model was not only better than the alternatives but also significantly predicted choice behaviour, I performed a logistic regression on work versus rest decisions including z-scored reward and z-scored interactions of effort and trial-by-trial model-estimated recoverable and unrecoverable fatigue as predictors (**Figure 9d**). As in the previous logistic regressions (with a Wilcoxon test across participants), reward significantly predicted choice ($p < .001$), but crucially there were also significant negative interactions of effort and both fatigue components (recoverable fatigue × effort: $Z = -4.98$, $p < .001$, 95% CI = [-4.93, -2.98]; unrecoverable fatigue × effort: $Z = -5.17$, $p < .001$, 95% CI = [-5.06, -3.39]). This was the case whether using the average estimated fatigue across participants (see **Figure 11**) or the model's idiosyncratic estimate of fatigue from each participant (all *p*s < .001). Thus, when the levels of fatigue in the model were higher, it was predictive of a greater tendency to rest, in particular when higher effort levels were on offer. Therefore, the willingness to exert effort for reward is not static but fluctuates moment-to-moment. When fatigue states in the model are higher this is related to reduced motivation and crucially a greater discounting of reward by effort.

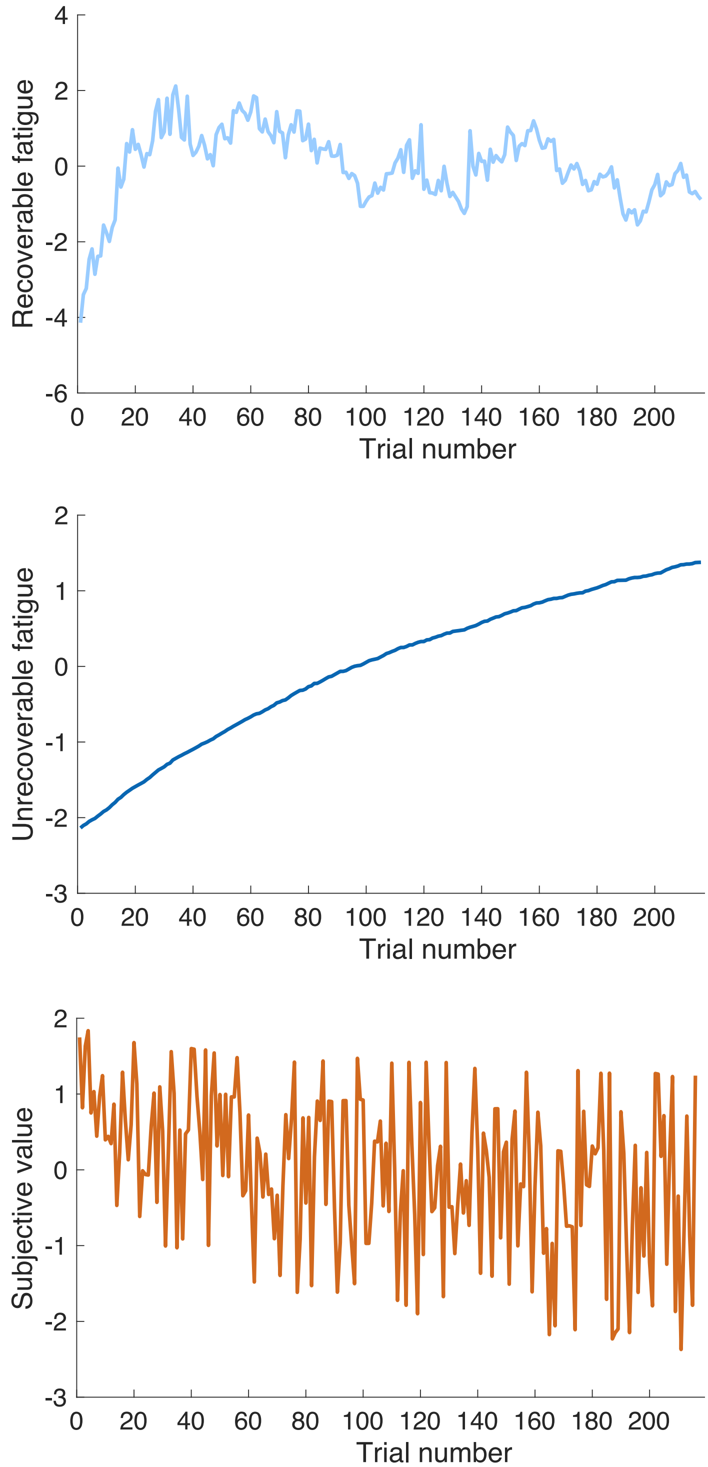

Figure 11. **Average (z-scored) model-estimated values from the full model.** Values for recoverable fatigue, unrecoverable fatigue and fatigue-weighted subjective value from the full model once fitted separately to all participants' data and then averaged and z-scored.

While it was assumed that the computational model was able to capture sensations of fatigue induced by effort and its effects on the value ascribed to exerting effort for reward, there are other factors that may correlate with the effects of fatigue within this model, such as boredom or the accumulation of reward. To demonstrate that this model was able to capture sensations of fatigue, I correlated the model parameters for each participant with the change in their subjective ratings of fatigue before and after the main task using Spearman's rank correlation coefficient. A significant correlation between the UF parameter (θ) and the change in rating was found (r_s = .361, two-tailed p = .033, 95% CI = [0.032, 0.620]). Participants showing a greater increase in ratings of fatigue had a higher parameter weight, suggesting a greater reduction in the willingness to exert effort for reward due to UF. No significant correlations were identified between the work and rest parameter weights defining RF and the change in ratings (RF work: r_s = .054, two-tailed p = .760, 95% CI = [-0.285, 0.380]; RF rest: r_s = .101, two-tailed p = .564, 95% CI = [-0.240, 0.420]), although such a result is to be expected as RF putatively only has short-term effects but ratings were taken more than one hour apart. These results suggest that choice behaviour in this task may have been linked to sensations of fatigue.

2.3.3 fMRI Results

It was hypothesised that regions of the brain previously linked to effort-based decision-making would be dissociable in terms of signalling different hidden states within the computational model. That is, the BOLD signal in some regions would fluctuate with levels of recoverable and unrecoverable fatigue. To test this notion, I fitted parametric trial-by-trial regressors of the model-estimated unrecoverable (UF) and recoverable fatigue (RF) time-locked to the moment when participants were presented with the work and rest offers. Although this was the moment when people were evaluating the work offer, these regressors carried information only about levels of fatigue - the history of exerted effort - and thus were not correlated with the effort level and reward of the work offer on the current trial. In addition, I examined activity covarying trial-by-trial with the model-estimated, fatigue-weighted subjective value of “work” (SV) at the time participants were presented with a choice. These parametric regressors were not strongly correlated ($r < 0.4$, see Methods) and thus activity independently covarying with each could be identified. Tables of results for all main analyses, including clusters with more than five voxels, are presented at an uncorrected threshold of $p < .001$ in **Tables 1 to 3**.

2.3.3.1 Distinct regions signal hidden fatigue states during decision-making

To test the hypotheses, I first examined whether distinct regions signalled motivational fatigue states on different timescales. I therefore examined voxels in which activity at the whole brain level and within the hypothesised regions of interest ([ROI] – see Methods) significantly covaried with parametric regressors reflecting the trial-by-trial values of RF, UF and SV. Then I tested whether the same voxels significantly covaried with one parametric regressor and did not significantly covary with the others. Such an approach of examining overlap avoids the problems of double-dipping in ROI based analyses. Thus, the results reported reflect a response exclusively to RF and UF.

A t-contrast on RF – to extract beta values corresponding to that regressor – revealed a significant negative relationship between the BOLD signal in a cluster extending across the posterior rostral cingulate zone (RCZp: 9, 5, 50; $Z = 3.57$, $p = .038$ small-volume correction [svc]; **Figure 12**). T-contrasts on UF and SV did not reveal voxels in this region for either contrast ($p > .001$ uncorrected). T-contrasts between RF and UF, as well as RF and SV, revealed significant clusters in the RCZp ($p < .05$ svc) overlapping with that showing a significant effect in the contrast on RF. Thus, at the time of evaluating and making effort-based decisions, activity in a region extending across the RCZp covaried negatively with a hidden *recoverable state* of fatigue that is increased through effort but recovered through rest.

A t-contrast on UF revealed a significant negative relationship with the BOLD signal in clusters in the left MFG of the DLPFC (**Figure 12** and **Table 2**) as well as in a cluster spanning the left anterior rostral cingulate zone (RCZa) and pre-SMA (-6, 20, 47; $Z = 3.67$; $p = .030$ svc; **Figure 12**). T-contrasts on RF and SV did not reveal voxels in the left MFG or RCZa for either contrast ($p > .001$ uncorrected). Contrasts between UF and RF, as well as UF and SV, revealed significant clusters in both the MFG and RCZa, albeit at a reduced threshold ($p < .05$), overlapping with those showing a significant effect in the contrast of UF above. Thus, a distinct portion of the ACC from that which signalled RF, showed an effect *of unrecoverable fatigue*, as did a portion of the MFG. Moreover, in both of these regions activity did not covary with the other components of the model. Thus, at the time of evaluating and choosing whether to exert effort for reward, RCZa and MFG activity negatively covaried with a gradually increasing state of fatigue that was associated with reductions in the motivation to work. In addition, a similar level of specificity was identified in a region of the insula in which activity positively correlated with UF (30, 17, 14; $Z = 4.67$; $p = .026$ FWE).

It has been suggested that signals in some regions linked to effort-based decision-making may signal the difficulty of the decision. Although different metrics of decision difficulty and conflict exist, I used the probabilities calculated by the softmax function as a metric of choice difficulty. Notably, activity in none of the regions outlined above covaried with decision difficulty ($p > .001$ uncorrected).

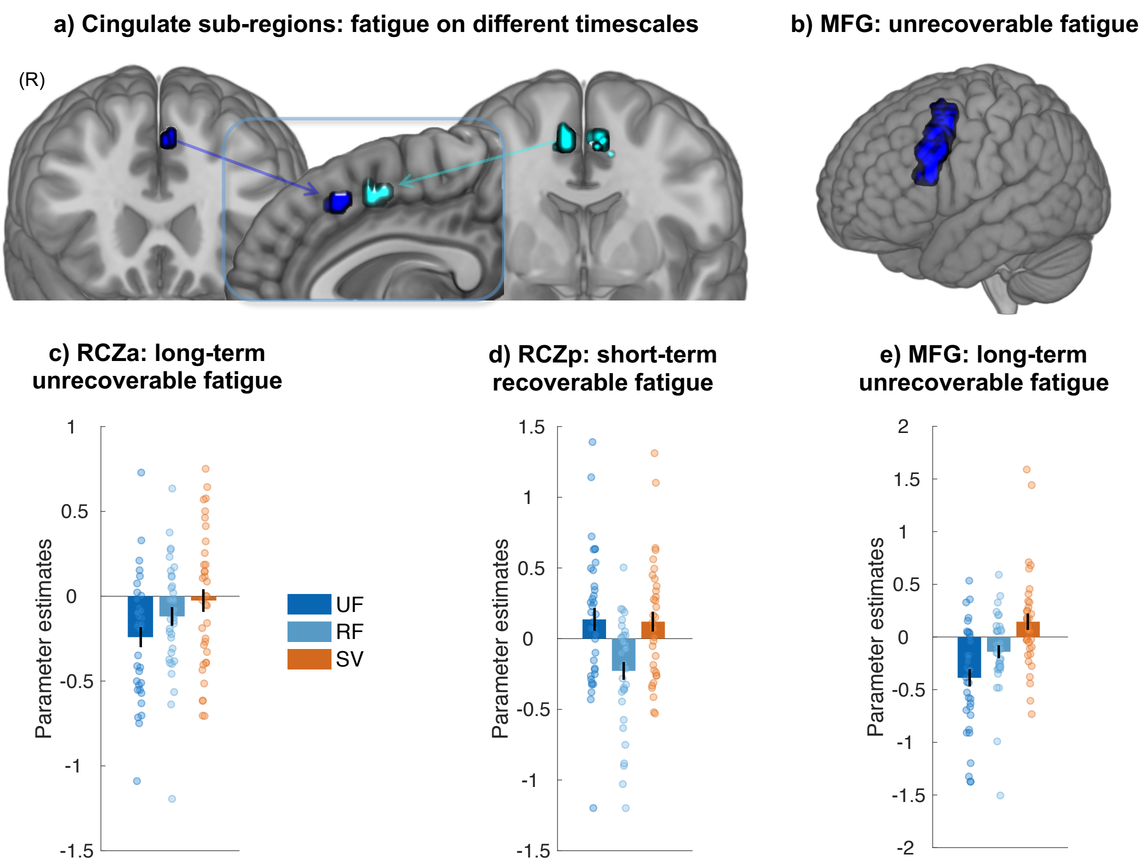

***Figure 12*. Hidden states of fatigue during effort-based decision-making. (a)** The BOLD signal in two distinct sub-regions of the ACC covaried trial-to-trial with unrecoverable (UF) and recoverable fatigue (RF) states estimated by the model. Overlay of clusters in the anterior rostral cingulate zone (RCZa; dark blue) with activity covarying with UF, and the posterior rostral cingulate zone (RCZp; cyan) with activity covarying with RF. Inset shows non-overlapping clusters. RCZ regions defined with respect to the parcellation of Neubert et al. (2015). **(b)** Activity in the middle frontal gyri (MFG) in which activity covaried with UF. Images displayed at $p < .001$ uncorrected. Parameter estimates (arbitrary units) at peak coordinates from RCZa **(c)**, RCZp **(d)** and MFG **(e)** for UF, RF and fatigue-weighted subjective value (SV). Each dot represents one subject. Error bars reflect SEM.

Table 1

Anatomical locations in which activity significantly covaried with recoverable fatigue, as derived from the computational model, at p < .001, uncorrected for multiple comparisons

Anatomical area	MNI peak	No. of voxels	Z-value	Voxel $p_{\text{uncorr.}}$
Right precuneus	24, -46, 26	12535	6.33	< 0.001*
Left inferior temporal gyrus	-42, -10, -34	14	4.02	< 0.001
Right anterior orbital gyrus	27, 41, -19	19	3.97	< 0.001
Right cuneus	6, -94, 20	11	3.84	< 0.001
Left anterior orbital gyrus	-15, 59, -16	6	3.82	< 0.001
Right precentral gyrus	39, -7, 62	42	3.68	< 0.001
Right temporal pole	42, 23, -37	18	3.58	< 0.001
Left temporal pole	-48, 17, -22	15	3.57	< 0.001
Right frontal pole	3, 65, -1	27	3.53	< 0.001
Left temporal pole	-33, 17, -37	23	3.44	< 0.001
Left angular gyrus	-36, -67, 41	14	3.40	< 0.001
Left precuneus	-18, -49, 50	26	3.39	< 0.001

Note. Coordinates are given in Montreal Neurological Institute (MNI) space (x, y, z). The asterisk indicates significance at a threshold of $p < .05$ with a whole-brain voxel-level family-wise error correction.

Table 2

Anatomical locations in which activity significantly covaried with unrecoverable fatigue, as derived from the computational model, at p < .001, uncorrected for multiple comparisons

Anatomical area	MNI peak	No. of voxels	Z-value	Voxel $p_{uncorr.}$
Left precuneus	-3, -67, 32	1852	5.18	< 0.001*
Left calcarine cortex	-12, -97, -1	1584	4.88	< 0.001*
Left middle frontal gyrus	-39, 8, 59	304	4.72	< 0.001*
Left middle temporal gyrus	-69, -37, -7	206	4.64	< 0.001*
Right middle temporal gyrus	69, -25, -10	62	4.43	< 0.001
Right angular gyrus	45, -67, 32	443	4.34	< 0.001
Brain stem	-3, -31, -37	46	3.98	< 0.001
Left middle frontal gyrus	-42, 47, -4	29	3.89	< 0.001
Right inferior temporal gyrus	57, -1, -34	16	3.69	< 0.001
Left RCZa / pre-SMA	-6, 20, 47	15	3.67	< 0.001
Right hippocampus	24, -19, -7	10	3.58	< 0.001
Right middle temporal gyrus	63, -10, -25	8	3.32	< 0.001
Left cerebellum	-6, -58, -16	6	3.27	< 0.001

Note. Coordinates are given in Montreal Neurological Institute (MNI) space (x, y, z). The asterisk indicates significance at a threshold of $p < .05$ with a whole-brain voxel-level family-wise error correction.

2.3.3.2 *A fronto-striatal system integrates value and fatigue*

Next, I examined activity that covaried with the fatigue-weighted value of the work offer estimated by the model (**Figure 13** and **Table 3**), using the same approach outlined above to identify activity that scaled only with SV. A t-contrast on SV revealed a significant positive relationship between the BOLD signal in the superior frontal gyrus (SFG) extending into the frontal pole (-12, 68, 17; $Z = 4.67$, $p = .025$ FWE) as well as in the ventral striatum, with the peak voxel within the nucleus accumbens of the Harvard-Oxford atlas (9, 11, -10; $Z = 4.31$, $p = .001$ svc). T-contrasts of RF and UF did not reveal voxels in this region for either contrast ($p > .001$ uncorrected). Contrasts between SV and RF, as well as SV and UF, revealed significant clusters in both FP and VS ($p < .05$ svc) overlapping with those showing a significant effect in the contrast on SV.

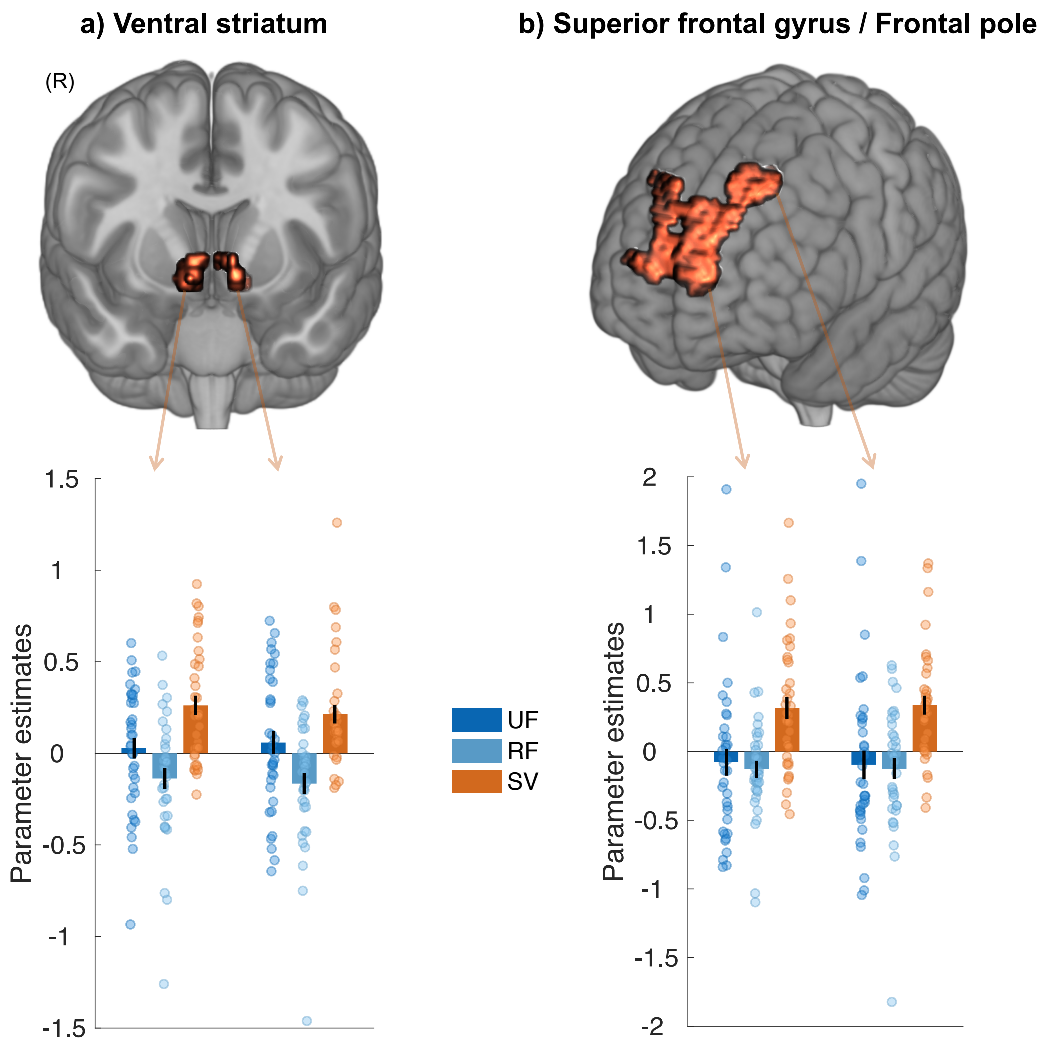

***Figure 13*. Fatigue-weighted subjective value in a fronto-striatal circuit. (a)** The BOLD signal in the ventral striatum (VS) covaried with model-estimated subjective value (SV), which is weighted by momentary levels of fatigue. Parameter estimates (arbitrary units) from peak coordinates for left and right VS (below) for the responses to SV, recoverable fatigue (RF) and unrecoverable fatigue (UF). **(b)** BOLD signal in superior frontal gyrus (SFG), extending across SFG/frontal pole areas 9 and 10, signals SV. Parameter estimates (arbitrary units) from peak coordinates in SFG/frontal pole (below) for the responses to SV, RF and UF. Each dot represents one subject. Error bars reflect SEM. Images displayed at $p < .001$ uncorrected.

Table 3

Anatomical locations in which activity significantly covaried with fatigue-weighted subjective value, as derived from the computational model, at p < .001, uncorrected for multiple comparisons

Anatomical area	MNI peak	No. of voxels	Z-value	Voxel $p_{uncorr.}$
Left cuneus	0, -88, 23	10344	5.75	< 0.001*
Left superior frontal gyrus	-21, 38, 50	390	4.73	< 0.001*
Right anterior orbital gyrus	21, 35, -7	73	3.91	< 0.001
Left temporal pole	-54, 14, -25	13	3.88	< 0.001
Left cerebellum	-27, -52, -55	29	3.77	< 0.001
Right medial frontal cortex	9, 44, -16	12	3.53	< 0.001
Right fusiform gyrus	39, -4, -28	9	3.49	< 0.001
Right superior temporal gyrus	48, -4, -13	9	3.49	< 0.001
Left inferior fontal gyrus	-54, 35, 11	6	3.33	< 0.001
Left occipital fusiform gyrus	-39, -79, -19	7	3.33	< 0.001
Right inferior temporal gyrus	60, -49, -16	8	3.30	< 0.001
Right lingual gyrus	18, -76, -13	9	3.23	< 0.001

Note. Coordinates are given in Montreal Neurological Institute (MNI) space (x, y, z). The asterisk indicates significance at a threshold of $p < .05$ with a whole-brain voxel-level family-wise error correction.

Consistent with the idea that activity in the VS was signalling fatigue-weighted value in a subjective manner, I also found significant correlations between the strength of signalling in the VS for UF and RF and each participant's corresponding parameter weights (α, θ, δ) from the model. To avoid double-dipping, I performed an independent analysis to identify voxels in which SV related activity correlated with parameters from the computational model. I found that the degree to which the VS signalled UF covaried with the unrecoverable fatigue parameter (θ; 6, 5, -7; $Z = 4.55$; $p = .043$ FWE). In addition, the degree to which the VS signalled RF correlated with the effect of rest on the recoverable fatigue (δ; 9, 17, -10; $Z = 3.36$; $p = .028$ svc) and the effect of effort on recoverable fatigue, albeit at a reduced threshold (α; 9, 17, -10; $Z = 2.93$; $p < .005$ uncorrected). No such effects were found in voxels in the other ROIs, with individual differences in fatigue and value only reflected in the VS response. Thus, a distinct fronto-striatal system processed the current value of exerting effort to obtain rewards, integrating momentary levels of fatigue that modulate the value ascribed to working. In the VS, variability between people, in the degree to which the fatigue variables covaried with activity, correlated with the parameters from the model that dictated how much someone's motivation was under the influence of fatigue.

2.4 Discussion

Many of our daily activities require us to persist in deciding that rewards are worth the effort. However, studies examining effort-based decisions typically assume that motivation is static. Here, an effort-based decision-making paradigm was employed in which participants made a series of choices between two alternatives: a rest option for a low reward (1 credit) or a work option, requiring the exertion of one of three levels of grip force for one of three higher amounts of reward. Using computational modelling of effort-based choices, I showed that two hidden states, one longer-term unrecoverable and one short-term recoverable, impact on people's decisions to work and exert effort for reward on a trial-by-trial basis. When these levels of fatigue are higher, it leads to a decrease in the value of working, resulting in choices to rest, particularly when working will be higher in effort and lower in reward. The BOLD response in distinct regions of the frontal cortex covaried separately with these two hidden states, with the MFG and the RCZa signalling the unrecoverable component and a distinct RCZp region signalling the recoverable component of fatigue. These regions carried no information about the subjective value of working. Instead, activity in a distinct fronto-striatal system comprising the VS and the FP integrated the latent states to signal the current value of working weighted by levels of fatigue. These results highlight that the willingness to exert effort is not static, and changes in internal states may shift how much value we ascribe to working on a momentary basis. Moreover, different brain regions are involved in coding for different components of dynamic motivational states.

In this study, people's subjective valuations of exerting effort for reward shifted constantly. In particular, choices to work were avoided at reward and effort levels in the main task that participants had readily chosen to undertake in a pre-task where fatigue would not have accumulated. The results suggest that these changes in the willingness to work were reactive, as a result of changes in internal states, rather than related to pre-emptive shifts in valuation. Such a conclusion is supported by the fact that planning was prevented by the experimental design, with offers of effort and reward presented in a pseudorandom order. As such, participants could not plan for the offers to-be-presented in upcoming trials. In addition, the results showed that a model containing fluctuating fatigue components better explained choices than a model in which participants shifted their valuations before the main task, but then held them constant across it. Thus, participants' willingness to work fluctuated and gradually declined across the main task. Offers that participants considered as worth working for at one moment would be rejected in favour of a rest at another.

This study unifies separate lines of research that have theorised that the effects of fatigue may occur on more than one timescale (Müller and Apps, 2019; Pessiglione et al., 2018), and provides a formalised account of their effects on effort-based decisions. One line of research had suggested that extended periods of work lead to exhaustion that has consequences for tasks performed after the one which caused the fatigue (Blain et al., 2016; Boksem et al., 2006; Inzlicht and Schmeichel, 2012; Lorist et al., 2005; Shigihara et al., 2013). This executive fatigue influences activity in the MFG in tasks performed after having been exhausted, an effect exacerbated in athletes who are over-trained (Blain et al., 2019, 2016). This form of fatigue appears to be unrecoverable in the sense that simply taking short rests does not have a restorative effect. Although in this study the possibility that this effect is simply due to time-on-task or boredom effects could not be fully ruled out, I was able to show that it affects effort-based decisions and may be related to changes in self-reported fatigue after as compared to before the task. Moreover, I showed that this longer-term effect is independent from a short-term recoverable component and that it covaries with activity during effort-based choice in the left MFG, largely overlapping with an area which has previously been associated with subjective aversion to cognitive effort (McGuire and Botvinick, 2010).

These results shed new light on this long-term, unrecoverable state. I showed that this component is indeed processed in the MFG during effort-based choice but builds slowly during extended, demanding tasks, reducing the willingness to exert effort for reward over an extended time period. Moreover, this effect is localised not only to the MFG but also to a connected sub-region of the cingulate lying in the RCZa (Balsters et al., 2016; Neubert et al., 2015; Vogt and Pandya, 1987). Lesions to this region reduce the motivation to exert effort in rodents (Walton et al., 2006) and neurophysiological recordings here have revealed neurons that respond to effort costs (Kennerley et al., 2009). Taken together, these findings would suggest that the MFG processes a longer-term accumulating fatigue that impacts both effort-based decision-making, performance, and choice behaviour in other tasks (Blain et al., 2019). In contrast, the RCZa processes similar information, but perhaps more specifically when deciding whether it is worth exerting effort. Moreover, the fact that activity negatively correlated with unrecoverable fatigue in RCZa with higher activity when fatigue was lower, and previous evidence that stimulating the RCZa causes a sensation of a willingness to persist through oncoming challenges (Parvizi et al., 2013), suggest the RCZa may play a key role in sustaining motivation and persisting during effortful tasks.

In addition, the present results highlight a short-term fatigue effect that crucially is recovered by taking rests. Such a component had long been theorised in accounts of physical fatigue (Meyniel et al., 2013; Müller and Apps, 2019; Van Cutsem et al., 2017). However, to date no study had directly examined the changes in neural activity that covary with changes in recoverable fatigue when people are choosing whether a reward and effort are “worth it”. A previous study had examined how people “gave up” and returned to work during continuous grip force (Meyniel et al., 2013) but did not examine how this influenced effort-based decisions, nor neural activity when ascribing value to work and making an effort-based choice. Here, at the time of making effort-based decisions I found computations of recoverable fatigue in the RCZp. This region has also previously been linked to persistence in decision-making tasks (Holroyd and McClure, 2015; Kolling et al., 2016b; Shenhav et al., 2013; Verguts et al., 2015), but here its role in signalling a short-term momentary fatigue state that influences decisions and the value of working was shown.

The findings presented here provide empirical evidence for theories which suggest that motivation fluctuates on a moment-to-moment basis, and they highlight the need for examining such momentary fluctuations to understand variability in cognitive processes over time. The notion of time-on-task effects in cognitively and physically demanding tasks is well known (Anderson et al., 2019;

Kurzban et al., 2013; Müller and Apps, 2019; Tanaka and Watanabe, 2012; van Duinen et al., 2007; Wylie et al., 2017). Accuracy and speed decline over time in many effortful cognitive tasks. However, the present results suggest that such changes in behaviour may be at least partially driven by a reduction in the value ascribed to persisting with exerting the effort required by the task demands. Considerable research has shown that task performance depends on the balance between the costs and benefits of acts. Rewards can increase the speed and accuracy of both movements and cognitive processes, by paying off the effort costs (Manohar et al., 2015; Shenhav et al., 2013). If the same difficulty of task is treated as more costly over time, as the model described here predicts, it will devalue rewards to a greater degree and reduce task performance. Whilst this study evaluated the willingness to work, rather than task performance, the results suggest that there could be moment-to-moment fluctuations in performance due to fluctuations in motivation happening on multiple timescales. Moreover, they point to a role of the VS for integrating current levels of fatigue with the value of persisting with a demanding task, and variability between people in such tendencies. A limitation of the experiment is that comparing value, without any influence of fatigue, to fatigue-weighted value signals is challenging, as they are necessarily correlated within the design. However, importantly, I found that variability in signalling in the VS between people correlated with the parameters of the computational model. Such a finding is consistent with activity in the VS signalling a dynamically changing estimate of value, which is weighted by each participant's tendency to persist in the face of momentary fatigue. Such effects would be missed or confounded by typical analysis approaches, e.g. when examining changes correlated with trial number or behaviour pre versus post exhaustion, but they can be examined using the formal framework outlined here. Future work will need to understand how the VS integrates fatigue and value-related information leading to fluctuations in the willingness to persist with ongoing behaviour.

A striking aspect of the results was that the different hidden internal variables of fatigue and value mapped on to activity in discrete brain regions, with each area processing information about a distinct component of the model. All of these regions – ACC, MFG, FP and VS – have previously been linked to the processing of effort and reward (Apps and Ramnani, 2014; Arulpragasam et al., 2018; Chong et al., 2017; Croxson et al., 2009; Hauser et al., 2017; Klein-Flügge et al., 2016; Kroemer et al., 2014; Kurniawan et al., 2013; Soutschek et al., 2018; Vassena et al., 2014; Verguts et al., 2015; Walton et al., 2006), but a considerable amount of this work, particularly that focused on the cingulate cortex, had assumed that valuations are static. The present results suggest that dynamic shifts in the valuation of effort correspond to changes in response across two sub-regions of the cingulate cortex, the RCZp and RCZa, and this information is integrated in the VS. Importantly, activity relating to fatigue does not explicitly represent the objective magnitude of the task difficulty. Indeed, responses in these regions covaried with the fatigue variables that carried no information about the reward and effort of the work offer. Rather, when activity in the RCZa and RCZp was reduced, it was at a time when levels of fatigue were higher, irrespective of the value of the offer. However, although both regions negatively correlated with levels of fatigue according to the model, they were dissociable, processing fatigue levels on different timescales. Such findings parallel recent evidence from studies examining how different parts of cingulate cortex are activated by learning at different timescales in reinforcement learning tasks (Meder et al., 2017). The present results suggest that this may be a wider ranging principal of organisation that extends to other types of decision variables in the cingulate cortex, with different aspects of fatigue shifting how effort and reward are valued in extended tasks.

It was beyond the scope of this investigation to examine whether the different components of motivational fatigue map onto purely psychological changes, physiological or metabolic changes in the state of the body, or fluctuations in neuromodulatory systems (Iodice et al., 2017b; Müller and Apps, 2019; Stahl, 2002). However, the computational approach taken here was able to best explain changes in decisions about whether to exert effort for reward, with the UF and RF components fluctuating in regions that have previously been linked to effort processing, rather than in regions that have been found to signal accumulated reward (Juechems et al., 2017; San-Galli et al., 2018). Future work will need to identify the source of these fluctuating, putative fatigue states, and disentangle them from other processes, such as opportunity cost processing, boredom, task switching and time-on-task.

Thus the model introduced here may be fruitful for examining such core questions relating to fatigue, including whether similar principles hold when using a cognitively effortful task (Dobryakova et al., 2013; Kool et al., 2010; Shigihara et al., 2013; Westbrook and Braver, 2015). By using a model that can quantify, idiosyncratically, each individual's sensitivity to the efforts they have exerted, and to their recovery through rest, variables underlying fatigue can be probed more precisely. Such an approach is also ideally suited for probing fatigue in the multitude of clinical disorders in which fatigue is present (Chaudhuri and Behan, 2004; Cullen et al., 2002). Future research may begin to examine how fatigue accumulates and subsides in clinical disorders, in order to develop more appropriate treatments for such a poorly understood symptom of disease.

2.5 Conclusion

Overall, this study provides insights into the neural and computational basis of the dynamics of motivation. The willingness to exert effort fluctuates on a moment-to-moment basis, with shifts in the value of exerting effort for reward depending on two hidden states of fatigue. These states covaried with neural activity in distinct brain regions previously linked to effort-based decision-making, namely in the RCZa and MFG, as well as in the RCZp, when making choices about whether exerting effort is worth for the reward. However, persistence also depended on a fronto-striatal circuit, which integrates fatigue and value, with variability in people's VS response predictive of the influence fatigue had on effort-based choice. These results reveal the hidden determinants of motivation that underlie persistence in the face of effort and provide a computational framework for the systematic assessment and quantification of motivation and fatigue in various disorders.

3 The role of preferences for effort or reward information

3.1 Introduction

Before deciding whether to exert effort for a particular reward, we first need to consider potential alternative options and gather information about the rewards associated with them and the effort required to obtain them. Such information gathering is dependent on attentional and perceptual processes (Krajbich et al., 2010; Manohar and Husain, 2013; Sinha et al., 2013), which in turn depend on both internal cues (e.g. long-term goals or current physiological state) and external cues (e.g. salient stimuli in the environment) (Bigliassi, 2015; Towal et al., 2013). While the precise mechanisms by which attention, information gathering and decision-making interact are still under discussion, studies which have tracked eye position have provided evidence that attention modulates the processing of information in favour of the information that seems most goal-relevant at any given moment (Sepulveda et al., 2020) and that attended information may receive greater weight in the decision-making process (Fisher, 2017; Krajbich et al., 2010).

What kind of information do people usually focus on before and during decision-making? Previous studies have shown that people may attend to the expected value of actions rather than to reward per se (Milstein and Dorris, 2007), while others found that reward associations and reward cues in the environment can attract attention and modulate gaze behaviour (Camara et al., 2013; Le Pelley et al., 2015). In contrast, a different line of research has suggested that during demanding physical exercise, attention may usually be focused on physiological sensations (Hutchinson and Tenenbaum, 2007; Tenenbaum and Connolly, 2008). As such, it could be assumed that the processing of information when making decisions about whether to expend effort for rewards may depend on context and potentially on interindividual characteristics, such as a person's sensitivity to efforts and level of motivation. Indeed, when decisions on the expenditure of physical effort (time cycling on an ergometer) to obtain rewards had to be made in a recent study, kinematic analysis of participants' mouse movements when they were deciding whether to exert effort or to rest revealed a bias to avoid high effort after compared to before exhaustion (Iodice et al., 2017a).

However, very little research has tested whether people prioritise knowing about the effort versus knowing the reward when gathering information about available options. In addition, even though a close relationship between information gathering and decision-making has been suggested, the two processes have mostly been investigated independently from one another. One recent study has aimed to investigate how people prioritise reward and effort information when making decisions (Vassena et al., 2019). In these experiments, people made a series of choices on whether to perform arithmetic calculations that varied in effort (easy versus hard) for varying amounts of rewards (small versus large). Crucially, information about the difficulty of the task and the magnitude of the reward (points) on offer was presented *consecutively*, with the first cue presented for a longer duration than the second one. The researchers found that when reward information was presented first, people were more likely to accept the offer. But comparison of choice behaviour with a condition in which both pieces of information were presented *simultaneously* suggested that people in general tend to prioritise effort information during decision-making. Yet, it remains unclear whether similar processes apply when people, instead of being externally cued, decide themselves which piece of information they want to look at first and whether these processes may potentially be related to subjective effort sensitivity.

In the present study I aimed to test whether people have an initial bias (preference) to seek out reward versus effort information before deciding whether to exert effort for reward, and whether this potential bias is associated with their willingness to work such that they weight the preferred information more highly. In particular, I hypothesised that a preference for effort information is related to higher effort discounting, i.e., an increased tendency to reject offers high in effort. Furthermore, I aimed to investigate potential sources of this bias, with a particular focus on the effect of previous choices and potential indices of effort sensitivity such as a person's general level of fatigue and motivation for vigorous physical activity. It was assumed that preferences might change based on recent choices, with preference for effort information as compared to reward information increasing after work, and that people who report being impacted by fatigue and doing less weekly exercise might show an increased preference for obtaining effort information prior to making their decision.

For this purpose, I developed a new physical effort-based decision-making task that assesses what kind of information people want to know first – the effort cost or the reward associated with an option – and how this preference is related to decisions to work. On each trial, before deciding whether to exert a certain amount of effort (force) for a certain reward (credits), participants were required to decide whether they first wanted to see the effort information or whether they first wanted to see the reward information. The task included five different effort levels and five different reward levels in order to precisely investigate effort discounting. To examine potential systematic interindividual differences, I explored the relationship between preferences in this task and self-reported fatigue and weekly physical activity using established questionnaire measures.

3.2 Methods

3.2.1 Participants

Forty young participants (24 females) with a mean age of 25.10 years (*SD* = 5.42; range 18-36) and with no history of neurological or psychiatric illness were recruited through the Oxford Psychology Research participant recruitment scheme and respective online bulletin boards. The study was approved by the local ethics committee, and written informed consent was obtained from all participants prior to the experiment in accordance with the ethical standards laid down in the Code of Ethics of the World Medical Association (Declaration of Helsinki).

3.2.2 Apparatus

The experiment was conducted in a laboratory room with only the participant and the experimenter present. Stimuli presentation and response collection were implemented using custom code in Matlab (The MathWorks, Inc., USA) and

Psychophysics Toolbox extensions (Brainard, 1997), controlled by a PC running the Windows operating system. To examine preferences for effort and reward information and their interaction with the willingness to exert effort, I developed a physical effort-based decision-making task, in which effort was operationalised as the amount of force exerted on a handheld dynamometer (TSD121B-MRI; BIOPAC Systems, Inc., USA). This allowed me to systematically set different, individualised effort levels and to compare the results from this experiment to the other experiments described in this thesis.

3.2.3 Experimental design and procedure

The experiment consisted of three parts (**Figure 14**): i) a *Calibration* phase to account for individual differences in strength, ii) a *Training* phase in which participants familiarised themselves with the effort levels used in this task, and iii) the *Main task*. In the Main task, participants decided on every trial whether they thought the credits on offer were worth the force level required to obtain them, with the total number of credits collected throughout the task determining their payment (range: £8 to £12).

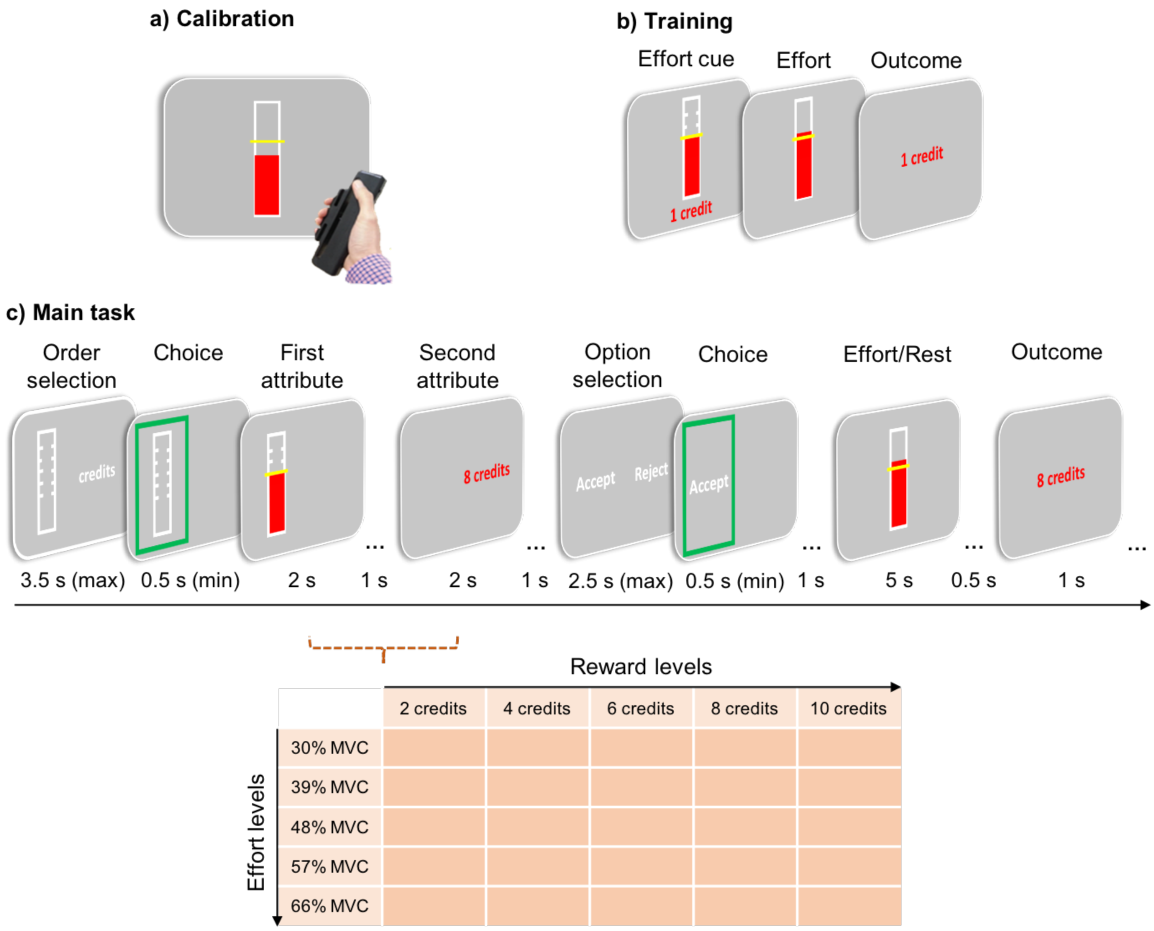

Figure 14. **Trial structure and experimental design. (a)** Each participant's maximum voluntary contraction (MVC) was obtained by asking them to exert as much force as possible on a handheld dynamometer while receiving real-time visual feedback. **(b)** Participants were trained to reach six levels of effort (0, 30, 39, 48, 57, 66% MVC) which were set depending on their individually calibrated MVC and indicated by a cue on each trial. **(c)** Trial outline for the Main task. Participants had to decide whether they first wanted to see the effort level required or the rewards on offer. The chosen option was highlighted by a green frame. Following this, participants received a variable offer of an effort/reward combination (ranging between 5x5 effort and reward levels), with effort and reward information presented successively, according to their choice. They then decided whether the credits were worth the effort, i.e. whether they wanted to accept or reject the offer. If participants accepted the offer, they had to squeeze above the required effort level for a minimum of 3 seconds in order to receive the offered credits while receiving real-time visual feedback on their force. Subsequently, they received feedback on the credits earned on that trial. If the offer was rejected, participants rested instead and received "1 credit". Note that only in a random 50% of the trials were participants required to squeeze above the effort level if they accepted the offer or to rest if they rejected the offer. All stimuli were presented on a black background. Dots represent blank screens.

During *Calibration* (**Figure 14a**), each participant's MVC was measured by squeezing a hand-held dynamometer on three consecutive trials with their dominant hand. Participants were required to apply as much force as possible on each trial, and they received strong verbal encouragement while squeezing. During each attempt, a bar presented on the screen provided real-time feedback of the force being generated. In the second and third attempts, a benchmark representing 105% and 110%, respectively, of the previous best attempt was used to encourage participants to improve on their score. The maximum level of force generated throughout the three attempts was used as MVC.

In the *Training* phase (**Figure 14b**), participants practised reaching each of six effort levels (0, 30, 39, 48, 57, and 66% of each participant's MVC). The trial was successful only when the force generated by the participant exceeded the required level for a sum total of at least 3 seconds in a five-second window. Practice of each effort level was repeated three times, resulting in 18 practice trials in total. Each trial commenced with a cue in the form of a bar, with a yellow line superimposed on the bar and a red filling indicating the upcoming effort level. To make sure that participants carefully and successfully completed this training, they were awarded one credit for each successful squeeze, while they received zero credits for a failure.

The *Main task* (**Figure 14c**) consisted of 75 trials, each requiring participants to make two decisions. In the first decision phase, participants were asked to decide whether they first wanted to receive information on the effort required or whether they first wanted to see information on the rewards on offer on that trial. In the second decision phase, participants had to decide whether they find the rewards on offer are worth the required effort. On each trial, one of five different effort levels that corresponded to 30, 39, 48, 57, and 66% of each participant's MVC and one of five different reward levels (2, 4, 6, 8, 10 credits) was presented. Effort and reward levels were similar to the ones used in the pre-task in **Chapter 2**, and they were varied independently and presented in a pseudo-random order to ensure that each effort/reward combination was distributed evenly across the task.

For the choice about what information to see first at the start of the trial, effort information was represented by a vertical bar on one side of the screen, and reward information was represented by the word "credits" on the other side of the screen. The location (left/right) of the two options representing the effort and reward information was randomised across trials to ensure that participants' potential preferences could be dissociated from a potential preference to always select the left or the right option. Participants had to respond within 3.5 seconds, pressing keys "b" and "n" on a keyboard with their index and middle finger, respectively, to select the left or the right option presented on the screen. Subsequently, according to the participant's choice, effort and reward information were presented successively, each for a duration of 2 seconds, separated by a blank screen presented for 1 second. Presenting both pieces of information for the same duration ensured that presentation order and presentation duration were not confounded. Information on the effort level was indicated by a yellow line superimposed on the bar and a red filling, while reward information was numerically displayed (number of credits). Participants then had to decide whether to reject the offer and rest for a low reward (1 credit) or whether to accept the offer and work for a higher reward. Again, the location (left versus right side of the screen) of the work

(“Accept”) and rest (“Reject”) option was randomised across trials. Responses had to be made within 2.5 seconds, pressing keys “b” and “n”, respectively, to select the left or the right option presented on the screen.

If participants chose to work, they were required to exert the required force on the dynamometer for at least 3 out of 5 seconds in order to receive the credits associated with the work offer. For this purpose, participants were presented with a vertical bar that provided them with real-time feedback on their force. The target effort level was indicated by a yellow line superimposed on the bar. If participants preferred to rest, the bar was presented for the same duration but with the yellow line displayed at the bottom of the bar. Following this, participants received feedback regarding their success or failure on that trial. The choice period in the following trial was separated from the outcome period in the preceding trial by an intertrial interval of 1 second. Note that if participants did not make a decision on their order preference for effort and reward information within the maximum response time given (first decision), they were allowed one second attempt. If they again failed to give a response, the remainder of the trial was skipped, and participants had to rest for 5 seconds without receiving any credits. In the current data set, the latter case never occurred.

Because the aim of this experiment was to assess reward discounting by effort in the absence of potential fatigue effects, only on a pseudo-randomly selected 50% of offers were participants actually required to exert effort. In the other cases, a screen with the text “Next trial…” was presented instead of the work or rest screen and the outcome screen for 1.5 seconds before the intertrial interval. Whilst participants were informed about this, they were instructed to always make their decisions as if they would have to squeeze if they chose the work option. Furthermore, the main task included two breaks, i.e., was split up into three blocks, and participants were free to decide when to continue with the task. The sequence of effort/reward combinations and the structure of the task were identical across participants to ensure that any potential differences in behaviour could be attributed to individual characteristics. Before the actual start of the main task, participants completed three practice trials to familiarise themselves with the task.

Prior to the main data collection, a few pilot participants were tested to ensure that instructions were easily understandable, that the reward and effort information was presented for long enough, that participants could easily differentiate between the different effort levels and that they had sufficient time to indicate their decisions. These participants were not included in the analyses.

3.2.4 Self-report questionnaires

Following completion of the task, participants were asked to fill out questionnaires assessing fatigue and physical activity and to provide some demographic information. In accordance with ethical guidelines and to increase the likelihood of participants responding honestly, they were free to skip individual questions if they felt uncomfortable answering them. Inspection of the data however indicated that every participant completed every question.

Fatigue was assessed using the Fatigue Severity Scale (FSS; Krupp et al., 1989). The FSS is a nine-item questionnaire assessing the degree to which someone has been impacted by fatigue over the past week by providing one score between 1 and 7. The FSS was first developed for use in patients and has subsequently been validated and administered across a wide range of disorders associated with fatigue, as well as in healthy people (Lerdal et al., 2005; Valko et al., 2008).

To examine a potential relationship between participants' behaviour on this task and their everyday physical activity, the short version of the International Physical Activity Questionnaire (IPAQ; Craig et al., 2003) was used, which aims to quantify physical activity in adults over the past seven days. Activity is categorized into *walking*, *moderate-intensity activities* (for example carrying light loads or bicycling at a regular pace), and *vigorous-intensity activities* (for example heavy lifting or fast bicycling). Scores are expressed in average MET-minutes/week for each type of activity, with MET representing the energy requirement of an activity as a multiple of the resting metabolic rate. To date, the IPAQ has widely been used across scientific studies and populations.

3.2.5 Statistical analysis

In the main analyses, choice behaviour was analysed with generalised linear mixed-effects models (GLMM) using the glmer function from the lme4 package (Bates et al., 2015b) in R 3.5.2 (R Core Team, 2018), while response times were analysed with linear mixed-effects models (LMM) using the lmer function from the same package with the maximum likelihood estimation method.

Using mixed-effects models allowed me to assess all trials and variables of interest within a single model, while accounting for potential variability between participants by including a subject-level random intercept. The inclusion or exclusion of factors was aimed at assuring a good balance between model interpretability, predictive accuracy and model complexity (Bates et al., 2015a; Matuschek et al., 2017). Choices to work or rest and choices to see effort information or reward information first were coded as binary variables. Trials with missed choices, which occurred very rarely such that no participant had missed more than two trials, were excluded from the analyses. Effort level, reward level and questionnaire scores were defined as continuous variables, with questionnaire scores being z-scored. Effects were tested for statistical significance using a Type II Wald chi-square test, i.e. χ^2 and *p*-values refer to comparisons between the tested model and the same model without the respective main effect or interaction of interest.

3.3 Results

3.3.1 No overall preference but within- and between-subject variability

First, I tested whether people in general tend to prefer knowing information on the effort associated with a work option first or whether they first wanted to know the reward that they could earn. Therefore, for each participant I calculated the number of trials on which they had chosen to see effort information first and the number of trials on which they had preferred to see reward information first and compared them with a non-parametric Wilcoxon signed-rank test. Overall, there was no statistically significant difference for choosing effort or reward information first before option selection, $Z = -0.440$, two-tailed $p = .660$. However, as indicated in **Figure 15**, there was considerable variability in participants' preferences to first see effort versus reward information, both intra-individually and inter-individually.

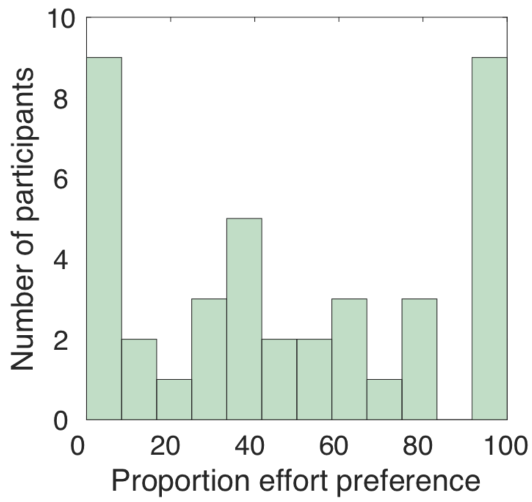

Figure 15. **General preference.** Depicted is the percentage of trials across the experiment in which a participant chose to first see the effort information of the work offer on that trial. The histogram illustrates variability in choosing effort or reward information first, both across and within participants.

3.3.2 Preferences predict option selection and response times

Next, to test whether a person's preference to first see the effort or the reward information on any given trial was predictive of the decision to expend the required effort for the offered reward or to rest, a GLMM on choices to work or rest on trials n was run with effort level, reward level and preference for information on trials n as well as all interactions as predictors. Analyses revealed a significant main effect of preference, $\chi^2(1) = 5.841$, $p = .016$, and a significant interaction of preference and effort level, $\chi^2(1) = 6.729$, $p = .009$, showing that choosing effort information first was associated with an increased likelihood of rejecting offers, in particular those high in effort (see also **Figure 16a**). Nevertheless, there were also significant main effects and a significant interaction of effort level and reward level (effort: $\chi^2(1) = 262.197$, $p < .001$; reward: $\chi^2(1) = 288.486$, $p < .001$; effort × reward: $\chi^2(1) = 4.374$, $p = .036$), demonstrating that participants considered both effort and reward information when deciding whether the reward on offer was worth the required effort and tended to reject high effort and low reward offers. All other interactions did not approach significance (preference × reward: $\chi^2(1) = 0.215$, $p = .643$; preference × effort × reward: $\chi^2(1) = 2.413$, $p = .120$; **Figures 16b** and **16c**).

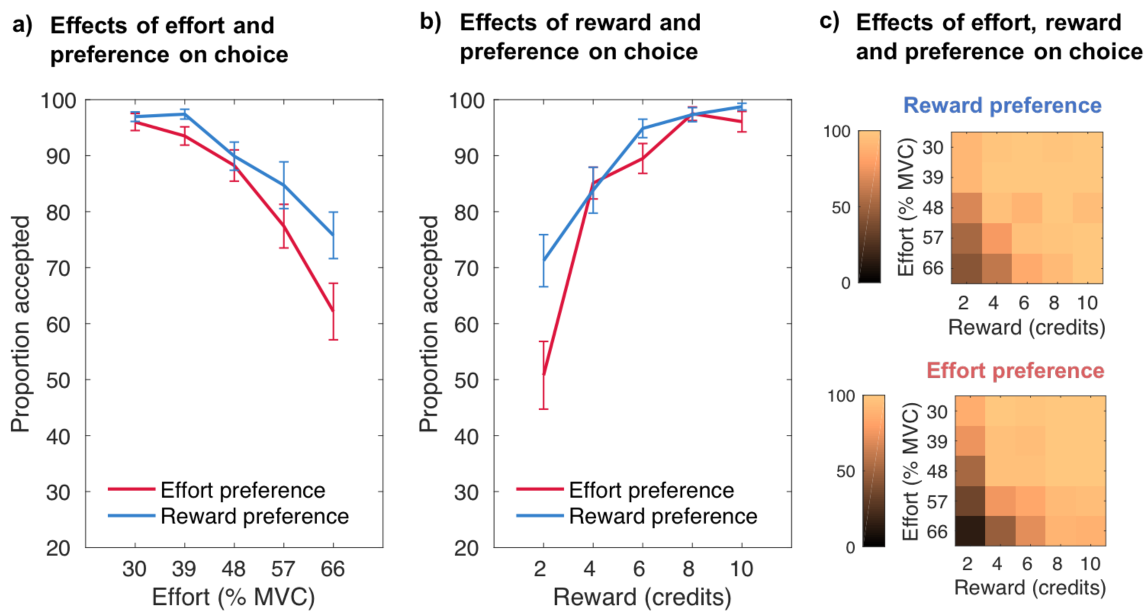

***Figure 16*. Choice behaviour towards working or resting dependent on participants' preferences on a trial.** Mean proportion of accepted work offers as a function of preference on a given trial, dependent on (a) the effort level, (b) the reward level, and (c) the effort and reward levels of the work offer. Reward preference depicts choice behaviour on trials on which participants chose to first see reward information, while effort preference depicts choice behaviour on trials on which participants chose to first see effort information. Error bars represent standard errors of the means.

To account for the variability between participants (see 3.3.1) and to further explore the effects, an additional GLMM was run in which for each participant the proportion of trials across the task on which effort information was chosen first (general preference) was included as a predictor instead of trial-by-trial preference. Similar to the results described above, the more often participants chose to see effort information first, the more likely they were to reject work offers, in particular those high in effort (general preference: $\chi^2(1) = 6.464$, $p = .011$; general preference × effort: $\chi^2(1) = 15.472$, $p < .001$; **Figure 17a**). In addition, the higher the effort level and the lower the reward level the more likely participants were to reject the offer (effort: $\chi^2(1) = 249.656$, $p < .001$; reward: $\chi^2(1) = 288.806$, $p < .001$; effort × reward: $\chi^2(1) = 5.058$, $p = .025$). All other interactions did not approach significance (general preference × reward: $\chi^2(1) = 0.205$, $p = .651$; general preference × effort × reward: $\chi^2(1) = 1.992$, $p = .158$; **Figures 17b** and **17c**).

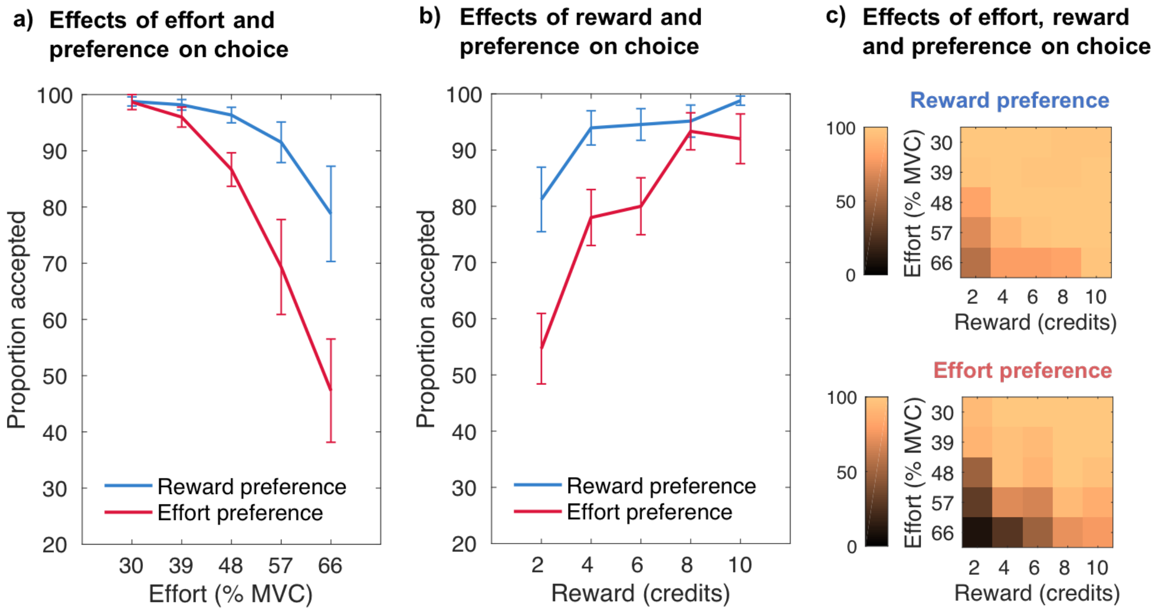

Figure 17. **Choice behaviour towards working or resting dependent on participants' general preferences.** Mean proportion of accepted work offers as a function of general preference, dependent on (a) the effort level, (b) the reward level, and (c) the effort and reward levels of the work offer. For illustration purposes, reward preference depicts choice behaviour from participants who chose to first see reward information in at least 80% of all trials, while effort preference depicts choice behaviour from participants who chose to first see effort information in at least 80% of trials. Error bars represent standard errors of the means.

In addition, I fitted the computational model, which was fitted to participants' choices in the pre-task in **Chapter 2**, to their choices in this task. The parameter dictating how much an individual discounts rewards by effort (k) was correlated with each participant's general preference using Spearman's rank correlation coefficient. The results revealed a significant positive relationship between a person's tendency to choose to see effort information first and this person's tendency to reject offers that would require the exertion of higher effort, $r_s = .369$, two-tailed $p = .019$.

To support these analyses and further investigate how preferences for effort or reward may affect choices, a separate LMM on participants' reaction times (RTs) in trials in which they had accepted the work offer was run, with effort level, reward level and preference for information on trials *n* as well as all interactions as predictors. Participants were slower to accept offers high in effort compared to offers low in effort, $\chi^2(1) = 29.043$, $p < .001$, and they were quicker to accept offers high in reward compared to offers low in reward, $\chi^2(1) = 17.339$, $p < .001$. The main effect of preference was not significant, $\chi^2(1) = 0.720$, $p = .396$, while the interaction of preference and effort level was close to being significant, $\chi^2(1) = 3.738$, $p = .053$ (see also **Figure 18a**). The other interactions did not approach significance (effort × reward: $\chi^2(1) = 1.237$, $p = .266$; preference × reward: $\chi^2(1) = 0.063$, $p = .801$; preference × effort × reward: $\chi^2(1) = 0.430$, $p = .512$; **Figure 18**).

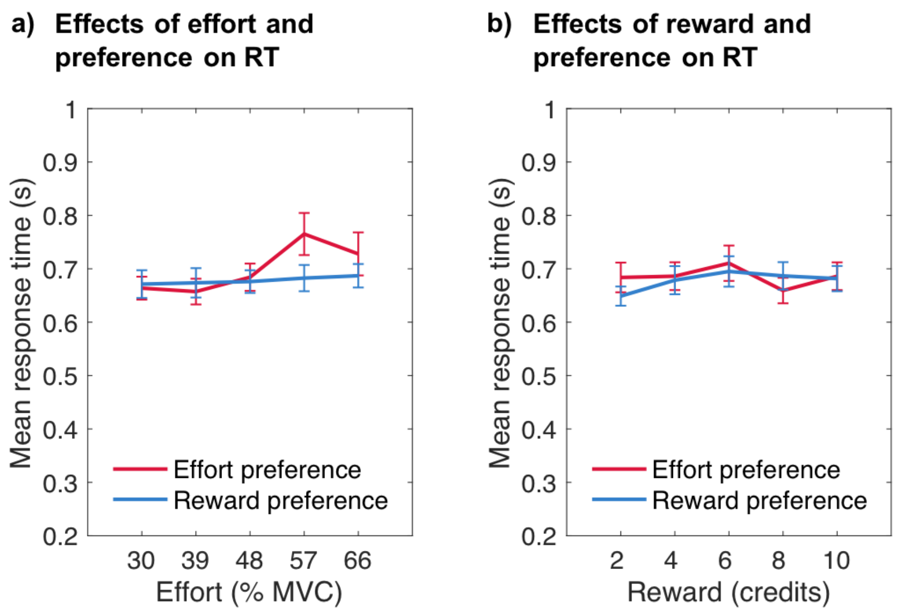

Figure 18. **Response times for accepted offers dependent on participants' preferences on a trial.** Mean response times (RTs) in seconds dependent on (a) the effort level and (b) the reward level of the work offer, as a function of preference on a given trial. Reward preference depicts response times on trials on which participants chose to first see reward information, while effort preference depicts response times on trials on which participants chose to first see effort information. Error bars represent standard errors of the means.

In an additional LMM in which preference was exchanged with general preference as predictor, when participants selected effort first in a high proportion of trials they were particularly slow in accepting higher effort offers (general effort preference × effort: $\chi^2(1) = 8.273$, $p = .004$; **Figure 19a**). There were also significant main effects of effort, $\chi^2(1) = 29.632$, $p < .001$, and reward, $\chi^2(1) = 18.385$, $p < .001$, but none of the other effects significantly predicted RTs when accepting work offers (effort × reward: $\chi^2(1) = 1.462$, $p = .227$; general effort preference: $\chi^2(1) = 0.355$, $p = .551$; general effort preference × reward: $\chi^2(1) = 0.191$, $p = .662$; general effort preference × effort × reward: $\chi^2(1) = 0.079$, $p = .778$; **Figure 19**). The finding that people who tended to prioritise effort information first were slower at accepting work offers that required exertion of higher effort than people who usually preferred to see reward information first provides further evidence that effort preference is associated with a bias against high effort options.

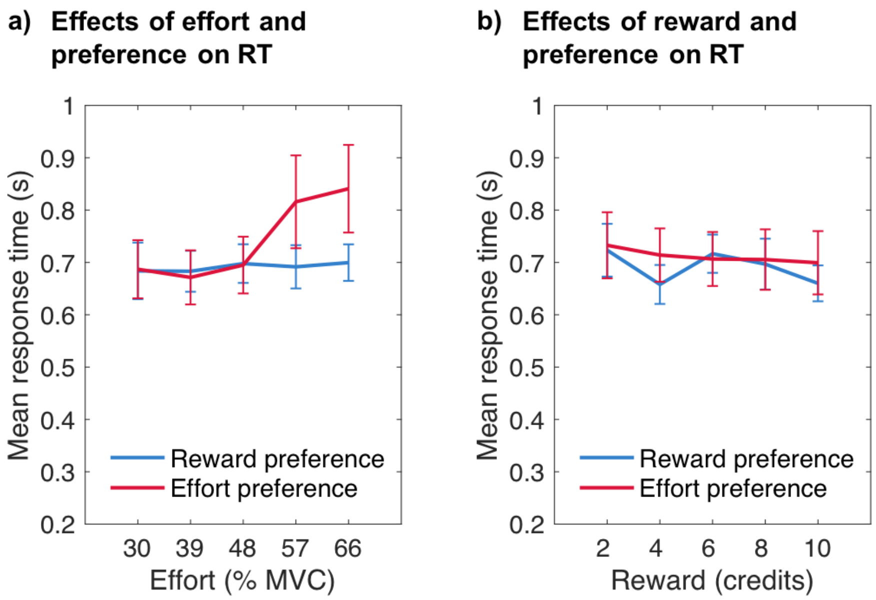

Figure 19. **Response times for accepted offers dependent on participants' general preferences.** Mean response times (RTs) in seconds dependent on (a) the effort level and (b) the reward level of the work offer, as a function of general preference. For illustration, reward preference depicts response times from participants who chose to first see reward information in at least 80% of all trials, while effort preference depicts response times from those participants who chose to first see effort information in at least 80% of trials. Error bars represent standard errors of the means.

3.3.3 Recent choices and general effort sensitivity predict preferences

Given the observed variability in preferences for effort versus reward information and the finding that preferences predicted effort-based decisions, I further examined which factors might be related to those preferences. First, I performed a GLMM on participants' trial-by-trial choices to examine how the decision to prioritise effort or reward information on trial *n* was affected by the choice to accept or to reject the work offer on trial *n*-1. In addition, I also examined how this was affected by measures of self-reported fatigue (FSS score) and weekly time spent with vigorous-intensity activities (IPAQ score). Analyses revealed that after having accepted a work offer, participants were somewhat more likely to choose to see effort information first, compared to after having rejected an offer, $\chi^2(1) = 3.983$, $p = .046$. Thus, trial-by-trial variability in choices to work or rest was predictive of trial-by-trial variability in preferences. Moreover, there was a significant interaction of self-reported fatigue and weekly vigorous activity, $\chi^2(1) = 6.097$, $p = .014$, indicating that in particular the combination of a high susceptibility to fatigue and a low tendency to do demanding exercise were associated with a preference to view effort information first. All of the other main effects and interactions did not reach significance (fatigue: $\chi^2(1) = 3.130$, $p = .077$; activity: $\chi^2(1) = 1.806$, $p = .179$; recent choice × fatigue: $\chi^2(1) = 0.004$, $p = .950$; recent choice × activity: $\chi^2(1) = 0.150$, $p = .698$; recent choice × fatigue × activity: $\chi^2(1) = 0.098$, $p = .754$).

To further examine the association between interindividual differences in preferences, fatigue and the willingness to expend physical effort, general effort preference, i.e. the percentage of trials in which effort information was chosen first by a participant, was correlated with the measures of fatigue and weekly time spent with physical activity. As the data was not normally distributed, Spearman's rank correlation coefficient was computed. Two-tailed *p*-values are reported. General effort preference was associated with higher self-reported fatigue severity, r_s =

.323, p = .042 (**Figure 20a**). In addition, there was a significant negative correlation between effort preference and a person's vigorous physical activity, r_s = -.391, p = .013 (**Figure 20b**). There were no significant correlations between general effort preference and weekly time spent with moderate physical activity, r_s = -.180, p = .267, or between general effort preference and weekly time spent walking, r_s = -.189, p = .242. These results indicate that people who become more easily fatigued with exercise and who do less vigorous intensity exercise tend to prioritise effort information more than people who are less susceptible to fatigue or who do more vigorous intensity exercise per week. A general focus on effort information might potentially amplify perceptions of fatigue and possibly result in avoidance of demanding work in everyday life.

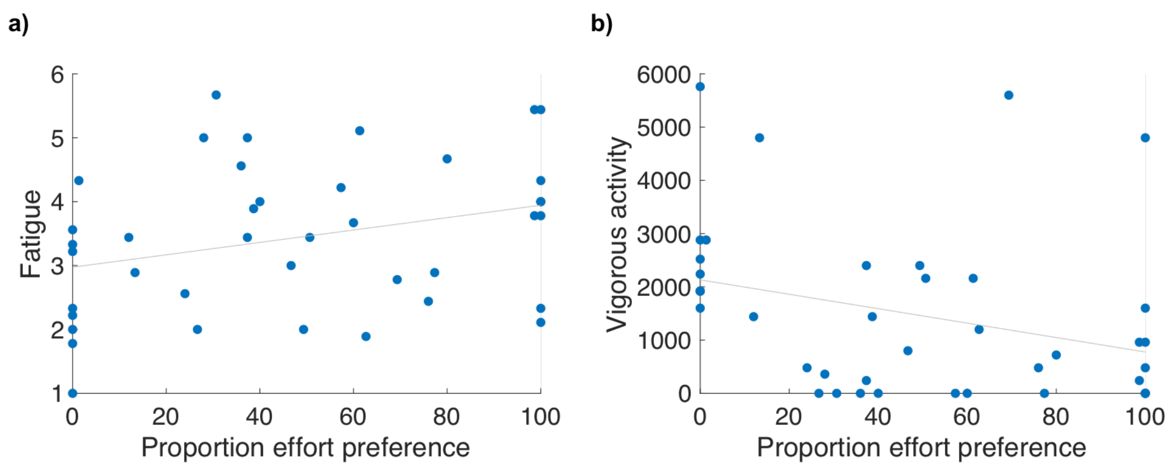

***Figure 20.* Correlation between general effort preference and effort sensitivity. (a)** Correlation between the percentage of trials in which a participant chose to first see the effort information and self-reported fatigue (FSS score). **(b)** Correlation between the percentage of trials in which a participant chose to first see the effort information and the intensity of vigorous activity undertaken, as assessed with the IPAQ. Vigorous activity is reported in MET-minutes per week.

3.4 Discussion

In this study, I investigated whether people have a systematic bias when gathering information about the rewards and about the effort associated with behavioural options, and whether this potential bias is associated with people's tendency to accept or reject those options. Before making decisions on whether to accept or reject a work offer, participants were required to decide whether they wanted to look at the effort on offer first or the reward on offer first. Results revealed that there was no overall preference for effort or reward information, but as hypothesised, the information which was chosen to be seen first predicted choices.

When participants chose to first see the effort information, they were more likely to reject offers that would require high effort, and even when they accepted the offer, they tended to have increased response times. This pattern was particularly evident in individuals who chose to see effort information first on the majority of trials. For most participants, preference for effort or reward information fluctuated on a trial-by-trial basis, while preferences for effort information tended to be higher after a work offer had been accepted. In addition, interindividual differences in fatigue and weekly time spent with vigorous physical activity were related to an individual's overall preference for effort or reward information.

First, these results provide evidence that attending to cost information first (versus last) is associated with reduced motivation. Here, this effect was in particular demonstrated in relation to effort and reward, where a preference to see effort information first was associated not only with a decreased willingness to exert high effort for reward but also with altered response times and was related to interindividual differences in weekly physical activity and fatigue severity. Notably, these effects were observed even though effort and reward information were presented for a similar duration in this experiment, highlighting the relevance of presentation order. While both effort and reward information were nonetheless taken into account when deciding whether exerting effort for reward was worth it, choosing to see effort information first might have placed a higher weight on the effort associated with the work offer and thereby have increased effort-discounting during subsequent decision-making. Speculatively, on the neural level, effort preference may have led to effort information being presented higher in the processing hierarchy, potentially in dorsolateral and medial prefrontal cortex (Vassena et al., 2019), or may have led to some sort of default value computation and choice in medial prefrontal cortex that then may or may not have been reversed (Arulpragasam et al., 2018). Thus, these findings extend previous research showing that prior preferences can bias choices (Hunt et al., 2016; Lopez-Persem et al., 2016) and that people are more likely to accept an offer when the reward information, as compared to the effort information, is seen first in a cognitive task (Vassena et al., 2019). But they also suggest that individual decisions to seek out and attend to information can affect the choice being made or the time taken to reach a decision.

Second, this study showed that preferences for effort or reward information may systematically change dependent on the recent choice history. Although there were several people who were relatively consistent in their preference for effort or reward information, participants tended to be more likely to focus on effort information than on reward information after having decided to work. Together with the finding that preferences on any given trial were related to the likelihood of working on the subsequent trial, the present results suggest dynamic trial-by-trial fluctuations in motivation, in particular in information gathering and effort-based decisions.

In addition, preferences for effort or reward information were associated with interindividual characteristics. The more participants had experienced an impact of fatigue in their daily life in the last week, and the less vigorous activity they were doing on a weekly basis, the more pronounced was their preference for effort information. These results stress that the preferences captured in this task are related to, and relevant for, everyday choices and behaviour. Again, speculatively on the neural level, differential attention to and amplification of effort or reward information might be associated with individual dopamine availability in the striatum, as suggested by recent studies on people's motivation to expend cognitive effort (Hofmans et al., 2020; Westbrook et al., 2020). While such a link between effort preference and effort-based choice could constitute an adaptive mechanism (Sepulveda et al., 2020; Stephan et al., 2016), simplifying decision-making and preventing exhaustion resulting from highly effortful behaviour, in some cases and over longer timescales however it might potentially lead to irrational choices and maladaptive, persistent effort avoidance (De Martino et al., 2006; Stephan et al., 2016).

Taken together, here it was shown that preferences for effort information and the willingness to exert effort were associated on a trial-by-trial basis and related to self-report measures of effort sensitivity. These results are in line with recent accounts and findings suggesting that fatigue may increase sensitivity to efforts during effort-based choices and bias decisions about whether to act (Iodice et al., 2017; Müller and Apps, 2019; Chapter 2). They thereby lend support to the concept that the fluctuating fatigue states, introduced in **Chapter 2**, are possibly linked to a respective fluctuating *effort bias*. That is, after work, effort sensitivity and fatigue supposedly increase, possibly directing attention more toward effort information, which may in turn lead to an increased likelihood of resting on the subsequent trial. Future work using a longer task in which effort is exerted on 100% of chosen work trials, and potentially in combination with forced work trials (ensuring that participants become fatigued during the task and that effects of effort, reward and rest can be specifically tested) would help to investigate this prediction of the interplay between fatigue, effort preference and effort-based choices over short and long timescales more closely.

Overall, the present study demonstrated that attention and information gathering processes play a significant role in effort-based decision-making, effortful behaviour and fatigue. Previous work suggested that optimised work-rest schedules could help ameliorate persistent forms of fatigue (Chaudhuri and Behan, 2004). The current findings might aid the development of new strategies for people to overcome maladaptive choice biases and maladaptive forms of behaviour, for example by carefully considering the presentation order of choice-relevant information or by systematically directing attention towards the rewards on offer.

3.5 Conclusion

This study revealed that preferences for effort or reward information can systematically vary on a trial-by-trial basis dependent on recent choices. It also showed that an individual's general effort sensitivity may be associated with a bias towards effort as compared to reward information before option selection, and that a focus on effort increases the likelihood of rejecting options that involve the expenditure of high effort. A better understanding of such choice biases and how they might develop into maladaptive forms (too little or too much focus on effort or rewards) may help prevent and improve abnormal decision-making, maladaptive behaviour and persistent fatigue in everyday life.

4 The influence of exertion, rest and reward on perceived effort and fatigue

4.1 Introduction

Within the course of a task, effortful exertion, rests and rewards have been shown to influence subsequent motivation, as outlined in **Chapter 2**, as well as people's performance in cognitively and physically demanding tasks (Boksem et al., 2006; Carroll et al., 2017; Enoka et al., 2011; Helton and Russell, 2015; Inzlicht et al., 2014; Mackworth, 1964; Meyniel et al., 2014, 2013; Pageaux and Lepers, 2016; Sidhu et al., 2013; Tanaka et al., 2014; Tanaka and Watanabe, 2012; Vøllestad, 1997; Warm et al., 2008). Previous accounts proposed that subjective sensations of fatigue might be crucial, decreasing motivation to continue with a task (Inzlicht et al., 2014; Kurzban et al., 2013; Müller and Apps, 2019).

Sensations of fatigue are classically thought to arise through effortful exertion, decline through taking rests and to be closely related to an altered subjective perception of effort that increases over extended or repeated exertion (Boksem and Tops, 2008; Chaudhuri and Behan, 2004; de Morree et al., 2014; Hockey, 2011; Krupp et al., 1989; Kuppuswamy, 2017; Marcora, 2009; Marcora et al., 2009; Meyniel et al., 2014; Müller and Apps, 2019; Pageaux, 2016; Pageaux and Lepers, 2016; Parry et al., 2011; Tanaka and Watanabe, 2012). Some researchers further assume that not only the amount of effort exerted but also other factors determine sensations of fatigue and thereby might play a role as well. According to studies on cognitive effort, perceived fatigue is a result of or a by-product of the potentially subconscious analysis of the predicted costs and benefits associated with exerting effort (Boksem and Tops, 2008; Wylie et al., 2017). In addition, higher perceived rewards and perceived control over one's daily work have been associated with lower perceived fatigue (Johnston et al., 2019).

In a recent laboratory experiment using a prolonged n-back task, performance and psychophysiological arousal measured through pupil diameter decreased, and subjective fatigue ratings increased with time-on-task, as measured over blocks of trials. However, when participants were informed that they could influence the remaining duration of the experiment dependent on their performance relative to previous blocks, their performance and arousal increased and fatigue ratings decreased again (Hopstaken et al., 2015). Thus, factors such as high personal control, goal proximity (being closer to the end of a task), and reduced opportunity cost (less time spent on a task) may have positively affected immediate performance and perceived fatigue. In addition, recent lines of research have suggested that monetary rewards may decrease perceived fatigue in healthy participants as well as in neurological patients (Dobryakova et al., 2020, 2018), and that the feeling of effort in a cognitive task may stem from the decision to exert effort (Bijleveld, 2018).

Similarly, research on physical exercise over the past four decades has pointed out that the perception of exertion is dependent on the actual work performed but to some degree may also depend on psychological factors and be modulated by attentional processes, especially when physical demands are not too high (Bigliassi, 2015; Blanchfield et al., 2014; Boutcher and Trenske, 1990; Lohse and Sherwood, 2011). However, in a recent experimental paradigm involving fast, alternating key presses participants tended to overestimate their effort when receiving higher compared to lower rewards, but only in cases in which a reliable relationship between rewards and the required effort level was inherent in the task (Pooresmaeili et al., 2015), stressing the level of exertion as a key factor.

Notably, very few studies have directly examined the effects of effort and reward on perceptions of fatigue, and subjective perceptions of effort, on a trial-by-trial basis. Existing studies have mostly examined feelings of effort or fatigue before and after a task or exercise, across tasks, across blocks of trials of a task, or across time intervals during exercise, making it difficult to precisely identify the underlying processes and computations. As a result, it is unclear whether the feeling of fatigue fluctuates, trial by trial, in a physical task in the same way that the willingness to exert effort does (see Chapter 2), limiting our understanding of both fatigue and motivation. Moreover, it is unclear whether the perception of effort increases over repeated exertion in a similar way, which would provide stronger evidence for the view that fatigue is associated with an increased perception of the costs of an action. In addition, there is a lack of research that systematically examines potential effects of rewards on perceived fatigue and on perceived effort in physical tasks.

In this study, I developed three tasks in order to systematically examine how sensations of fatigue and effort develop over repeated physical exertions as a function of effort exerted, rest taken, and rewards obtained. On every trial of these tasks, participants exerted a certain amount of effort (grip force) for a certain amount of reward and afterwards rated on a visual analogue scale how tired they felt (Experiments 1 and 2) or how hard they found it (Experiment 3). Crucially, effort and reward levels were varied independently across trials. While in Experiment 1, the reward on each trial was presented to participants *before* working or resting, in

Experiment 2 information on the reward associated with that trial was only presented to participants *after* they had worked or rested. This allowed for testing any effect of reward without any potential confound of behaviour such as participants possibly exerting more force when higher rewards are at stake (Bonnelle et al., 2016, 2015; Oudiette et al., 2019). Using forced work and rest trials in all three experiments ensured that I could also test whether the computational model outlined in Chapter 2 could explain the build-up of sensations of fatigue independently of motivation. In addition, factors affecting perceived effort and fatigue could be tested here without the need for participants to explicitly make cost-benefit computations which may have biased previous results.

Here, I hypothesised that sensations of fatigue increase dependent on the amount of physical effort exerted and decrease as a function of time rested, that they are best characterised by recoverable (RF) and unrecoverable (UF) components, and that overall they may change independently of reward. Given the close association between effort and fatigue, effort ratings were hypothesised to develop in similar ways, with higher ratings on high effort trials and an increase in effort ratings over repeated exertion.

4.2 Methods

4.2.1 Participants

Young participants were recruited through the Oxford Psychology Research participant recruitment scheme and online bulletin boards. For Experiment 1, the sample consisted of 40 participants (24 females) with a mean age of 24.18 years (*SD* = 4.68; range 19-35) and with no history of neurological or psychiatric illness. For Experiment 2, a new sample of 41 individuals participated of which one reported psychiatric illness and was therefore excluded from the analyses. The final sample of 40 participants comprised 24 females and had a mean age of 25.53 years (*SD* = 5.63; range 18-40). A new sample of 42 individuals participated in Experiment 3 of which one reported psychiatric illness and was excluded from the analyses. The final sample of 41 participants who did not report any history of neurological or psychiatric illness comprised 21 females and had a mean age of 23.93 years (*SD* = 5.18; range 18-40). The studies were approved by the local ethics committee, and written informed consent was obtained from all participants prior to the experiment in accordance with the ethical standards laid down in the Code of Ethics of the World Medical Association (Declaration of Helsinki).

4.2.2 Apparatus

The experiments were conducted in a laboratory room with only the participant and the experimenter being present. Stimuli presentation and response collection were implemented using custom code in Matlab (The MathWorks, Inc., USA) and Psychophysics Toolbox extensions (Brainard, 1997), controlled by a PC running the Windows operating system. To examine effects of effort and reward on perceived fatigue and on perceived effort on a trial-by-trial basis, I developed a task in which effort was operationalised as the amount of force exerted on a handheld dynamometer (TSD121B-MRI; BIOPAC Systems, Inc., USA). This allowed me to systematically set different, individualised effort levels. To reduce discomfort, the dynamometer was padded with "squash" tape.

4.2.3 Experimental design and procedure

The experiment consisted of three parts (**Figure 21**): i) a *Calibration* phase to account for individual differences in strength, which was completed before the experiment was explained in full to the participants, ii) a *Training* phase in which participants familiarised themselves with the effort levels used in this task, and iii) the *Main task*. In the Main task, participants were asked on every trial to rest or to exert force for rewards (credits). Effort and reward levels were identical to the ones used in the Main task in **Chapter 2**. This ensured comparability between tasks, and the use of low to intermediate effort levels in addition ensured that participants were able to successfully complete this task and that potential effects of outcome uncertainty were mitigated. Subsequently, participants were asked to rate on a visual analogue scale how fatigued they felt (Experiments 1 and 2) or how effortful they found the trial (Experiment 3). Participants were instructed to collect as many credits as they could throughout the experiment, with the total number of credits collected across the task determining their payment. That is, participants were paid £8 for their time and received a bonus payment of up to £4 which was proportional to the credits they had earnt in the task. Prior to the main data collection, a few pilot participants were tested to ensure that participants were willing and able to successfully complete the task without becoming fully exhausted and that enough time was given for them to change their ratings accordingly. The pilot participants were not included in the analyses.

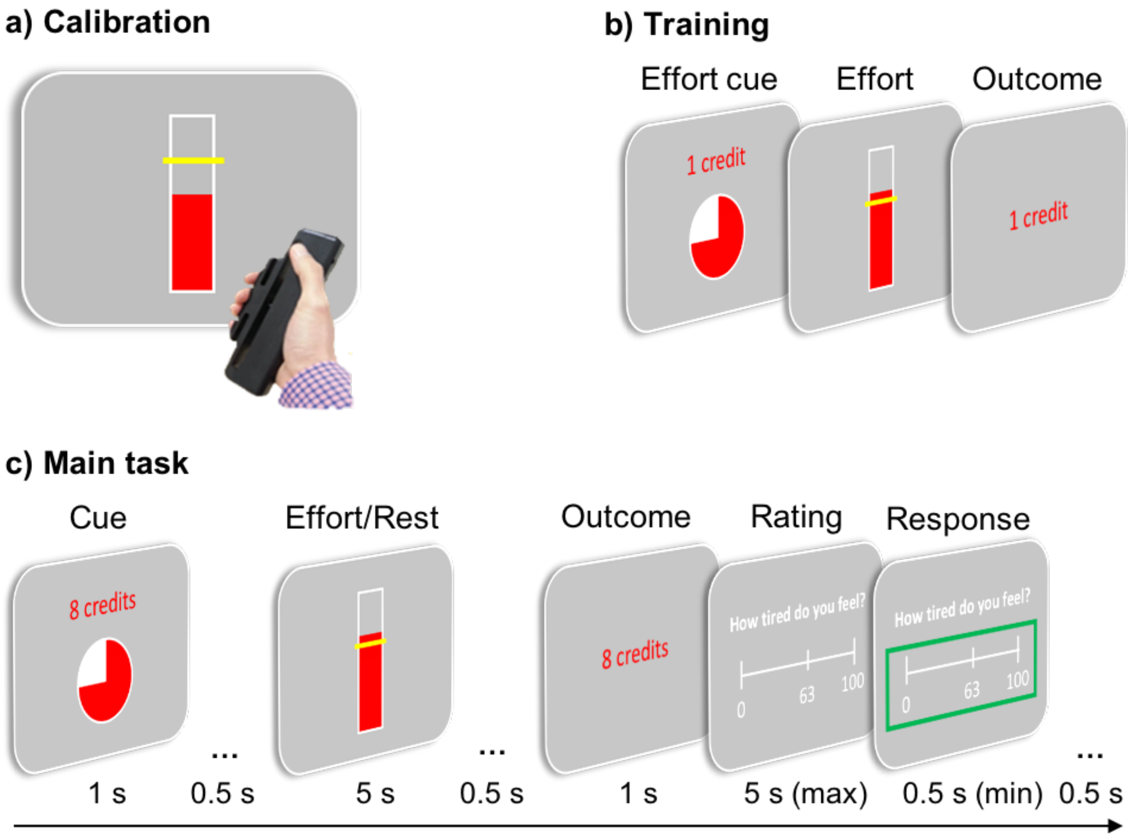

Figure 21. **Illustration of the different parts of the experiment. (a)** Each participant's maximum voluntary contraction (MVC) was obtained by asking them to exert as much grip force as possible on a handheld dynamometer while receiving real-time visual feedback. **(b)** Participants were trained to reach four levels of effort which were set depending on their individually calibrated MVC (0, 30, 39, and 48% of each participant's MVC). On each trial, a cue first indicated the effort that participants subsequently had to exert. **(c)** Trial outline for the Main task (Experiment 1). Participants were presented with a cue indicating how much effort they had to exert (rest or one of three possible effort levels) and the rewards they could earn on that trial (6, 8, or 10 credits). They then either had to rest or to squeeze above the required effort level (i.e. the required proportion of each participant's previously determined MVC) using a handheld dynamometer for a minimum of 3 seconds in order to receive the credits. For this purpose, participants were presented with a vertical bar, providing them with real-time feedback on their force (red filling) and indicating the target level by a yellow line superimposed on the bar. Subsequently, they received feedback on the credits earned on that trial and were then asked to rate on a visual analogue scale ranging from 0 to 100 how tired they are feeling. All stimuli were presented on a black background. Dots represent blank screens. In Experiment 2, the cue did not provide any information on the credits associated with the trial. Experiment 3 was identical to Experiment 1, but participants were asked to rate instead how hard they found the trial on a visual analogue scale ranging from 0 to 20.

During *Calibration* (**Figure 21a**), each participant's MVC was measured by squeezing a hand-held dynamometer on three consecutive trials with their dominant hand. Participants were required to apply as much force as possible on each trial, and they received strong verbal encouragement while squeezing. During each attempt, a bar presented on the screen provided feedback of the force being generated. In the second and third attempts, a benchmark representing 105% and 110%, respectively, of the previous best attempt was used to encourage participants to improve on their score. The maximum level of force generated throughout the three attempts was used as MVC.

In the *Training* phase (**Figure 21b**), participants practiced reaching each of four effort levels (0, 30, 39, and 48% of each participant's MVC). The trial was successful only when the force generated by the participant exceeded the required level for a sum total of at least 3 seconds in a five-second window. Each trial commenced with a cue in the form of a pie chart, with the number of red segments indicating the upcoming effort level. To make sure that participants carefully and successfully completed this training, they were awarded one credit for each successful squeeze, while they received zero credits for a failure. In an additional four trials, participants practiced manipulating the rating scale before they completed four full practice trials consisting of the different effort levels and a rating (see Main task) in order to familiarise themselves with the task.

The *Main task* (**Figure 21c**) consisted of 120 trials, each requiring participants to either rest or work for credits. In Experiments 1 and 3, work trials consisted of one of three different effort levels, represented by two to four filled segments in a pie chart (cue) that corresponded to 30, 39, and 48% of each participant's MVC, and one of three different reward levels as numerically displayed below the pie chart (6, 8, or 10 credits). Rest trials were indicated by one filled segment in a pie chart and the number of credits (6, 8, or 10) numerically displayed below it. Experiment 2 was identical to Experiment 1 except for the fact that the cue only indicated the upcoming effort level but not the reward level. In Experiment 2, rewards were presented for 1.5 seconds and only shown to the participants after they had worked or rested on that trial. In all experiments, effort and reward levels were varied independently and presented in a pseudo-random order to ensure that each effort/reward combination was distributed evenly across the task, and each participant was presented with the same sequence to ensure that any potential differences in behaviour could be attributed to individual characteristics.

After this cue, representing the upcoming effort and – in Experiments 1 and 3 – reward levels, participants were required to rest or to exert the respective force on the dynamometer for at least 3 out of 5 seconds in order to receive the credits. For this purpose, they were presented with a vertical bar that provided them with real-time feedback on their force. The target effort level was indicated by a yellow line superimposed on the bar. If participants had to rest on that trial, the bar was presented for the same duration but with the yellow line displayed at the bottom of the bar. Following this, participants were shown the credits they had obtained dependent on their success or failure on that trial.

In Experiments 1 and 2, participants then were asked to indicate how tired they feel on a scale ranging from 0 to 100, with 0 representing *not tired at all* and 100 representing *completely exhausted*. Immediately before the first trial, participants were given as much time as they needed to indicate how tired they currently felt (baseline rating). On each subsequent trial, the starting value on the scale was the value the participant had entered on the previous trial, and participants had a maximum of 5 seconds to either confirm or change this value. In Experiment 3, participants were instead instructed to answer the question "How hard did you find this?" on a scale ranging from 0 to 20, with 0 representing no effort at all and 20 representing maximum effort. The starting value on the scale was randomised across the task but identical across participants, and they had a maximum of 5 seconds to either confirm or change this value.

Participants could change the value on the rating scales in increments of 1 by using the left and right arrow keys on a keyboard. They then confirmed their chosen value by pressing the downward arrow key, which was indicated by a green frame appearing around the rating scale. To ensure that participants reported their perceptions accurately, it was made clear to them that none of their ratings would have an effect on the task they were asked to complete.

4.2.4 Statistical analysis

To examine how people's sensations of fatigue and effort change on a trial-to-trial basis, I first analysed changes in participants' fatigue ratings from trial *n*-1 to trial *n* (Experiment 1 and 2) or participants' effort ratings on trial *n* (Experiment 3) with linear mixed-effects models (LMM) using the lmer function from the lme4 package (Bates et al., 2015b) in R 3.5.2 (R Core Team, 2018) with the maximum likelihood estimation method. In addition, I examined their behaviour (force produced) on trial *n* (all experiments) using similar models. Force on each trial was calculated as the area under the curve of the voluntary contraction trace recorded from the dynamometer, using the *trapz* function in Matlab. For every participant, the area under the curve on any given trial was normalised by the maximum value calculated for this participant to account for interindividual differences in force exerted.

Trials *n* in which participants worked and trials *n* in which they rested were examined in separate LMMs. This was based on the assumption that changes in fatigue or perceived effort would be (linearly) scaled by the amount of force when they exerted force, while taking rests might have a differential impact on the perception of effort and fatigue, as also indicated by the results of Chapter 2. Only trials *n* in which participants had successfully reached the effort level for the required duration and thus obtained the credits were included in the models. Overall, this resulted in the exclusion of $M = 1.81\%$ ($SD = 4.51$) trials in Experiment 1, $M = 4.21\%$ ($SD = 6.60$) trials in Experiment 2, and $M = 3.07\%$ ($SD = 6.76$) trials in Experiment 3. In all models, a subject-level random intercept was included which allowed modelling of potential variability between participants. The inclusion (and exclusion) of predictors, interactions and additional random slopes was chosen to assure a good balance between model interpretability, predictive accuracy and model complexity, determined by model convergence and by model fit as indicated by AIC (Bates et al., 2015a; Burnham and Anderson, 2004; Matuschek et al., 2017). Therefore, in all analyses of work trials, a random slope for force (or effort level) was included. Trial number was added as an additional predictor to account for potential confounds, such as a potential reduction in force or in the manipulation of the rating scale over the course of the task, e.g., in cases in which participants had reached the upper limit of the rating scale before the end of the experiment. Dependent variables and predictors were coded as continuous variables. Effects were tested for statistical significance using a Type II Wald chi-square test, i.e. χ^2 and *p*-values refer to comparisons between the tested model and the same model without the respective main effect or interaction of interest.

4.2.5 Computational modelling

4.2.5.1 Modelling trial-by-trial fatigue ratings (full model)

In addition, to more specifically predict and quantify the effects of exertion and rest on fatigue on a trial-by-trial basis and to test whether the computational model fitted to choices in **Chapter 2** could also explain changes in fatigue ratings induced by effort and rest, I fitted the five computational models that predicted fatigue effects (see Chapter 2) to each participant's fatigue ratings in Experiments 1 and 2. Force was calculated as described under 4.2.4. The full model assumed that fatigue would increase with exertion and would be partially recoverable and decrease with time spent resting but would also have a gradually increasing unrecoverable component which did not recover with the rest taken in a trial. On each trial t, fatigue (F) was calculated as the sum of a participant's baseline fatigue rating (F_{start}), recoverable fatigue (RF) and unrecoverable fatigue (UF):

$$F_{(t)} = F_{\text{start}} + RF_{(t)} + UF_{(t)} \quad (9)$$

RF increases dependent on the force, multiplied by 10, exerted (E) on a trial (Equation 10) and decreases dependent on the time rested (T) on a trial (Equation 11):

$$RF_{(t)} = RF_{(t-1)} + (\alpha * E_{(t)}) \tag{10}$$

$$RF_{(t)} = RF_{(t-1)} - (\delta * T_{(t)}) \tag{11}$$

Individuals differ in the degree to which effort increases their fatigue, as reflected by the subject-specific parameter α, and in how quickly they recover during rest, reflected by the parameter δ. Unlike RF, UF accumulates depending on the effort exerted across the whole task and is not restored by resting during a trial (Equation 12). The parameter θ represents how quickly different individuals build up fatigue that cannot be easily recovered.

$$UF_{(t)} = UF_{(t-1)} + (\theta * E_{(t)}) \tag{12}$$

Initial RF and UF values were set to 0, with RF and UF subsequently updated on each trial according to the respective model and added to the fatigue level indicated by the respective participant before the start of the main task (baseline rating). Based on theoretical considerations, only parameter values (α, δ, θ) >= 0 were allowed.

The fit between the model and the data, as indexed by the sum of squared residuals between the participant's ratings and the model's estimates, divided by the model's estimates, was optimised using the *fminsearch* function in Matlab, i.e. model parameters were changed to minimise the difference between each participant's actual fatigue rating and the fatigue rating predicted by the model for each trial. To maximise the chances of finding global rather than local minima, parameter estimation for the full model and for all alternative models was repeated over a grid of initialisation values, with 6 initialisations (ranging from 0 to 1) per parameter. The optimal set of parameters for each model was used for model comparison.

4.2.5.2 Model comparison

To verify whether the three parameters used to quantify the effects of effort and rest were necessary, alternative models were also fitted to participants' ratings. This included models in which there was a UF component only (i.e. θ being fitted) or an RF component only (i.e. α and δ being fitted). In addition, two further mathematically plausible but theoretically unlikely models were included which used only one parameter to scale the effect of effort and rest on recoverable fatigue (i.e. only α being fitted across both work and rest trials). In one of these models, fatigue was only comprised by this one parameter RF, while in a second model, fatigue comprised UF plus the one parameter RF. In order to investigate the models' relative ability to predict the behavioural data, model fits were compared using AIC and BIC with lower values indicating better fit. AIC and BIC were calculated by adding a penalty term to the model fit which depended on the number of parameters and in the case of BIC also on the number of observations, i.e. the number of trials, as outlined in **Chapter 2**.

4.3 Results

4.3.1 Experiments 1 and 2

4.3.1.1 Perceived fatigue primarily depends on exertion and rests

First, I examined whether feelings of fatigue increased over the course of the task. Indeed, participants' fatigue ratings on a visual analogue scale ranging from 0 to 100 increased in both Experiments 1 and 2 (**Figure 22**).

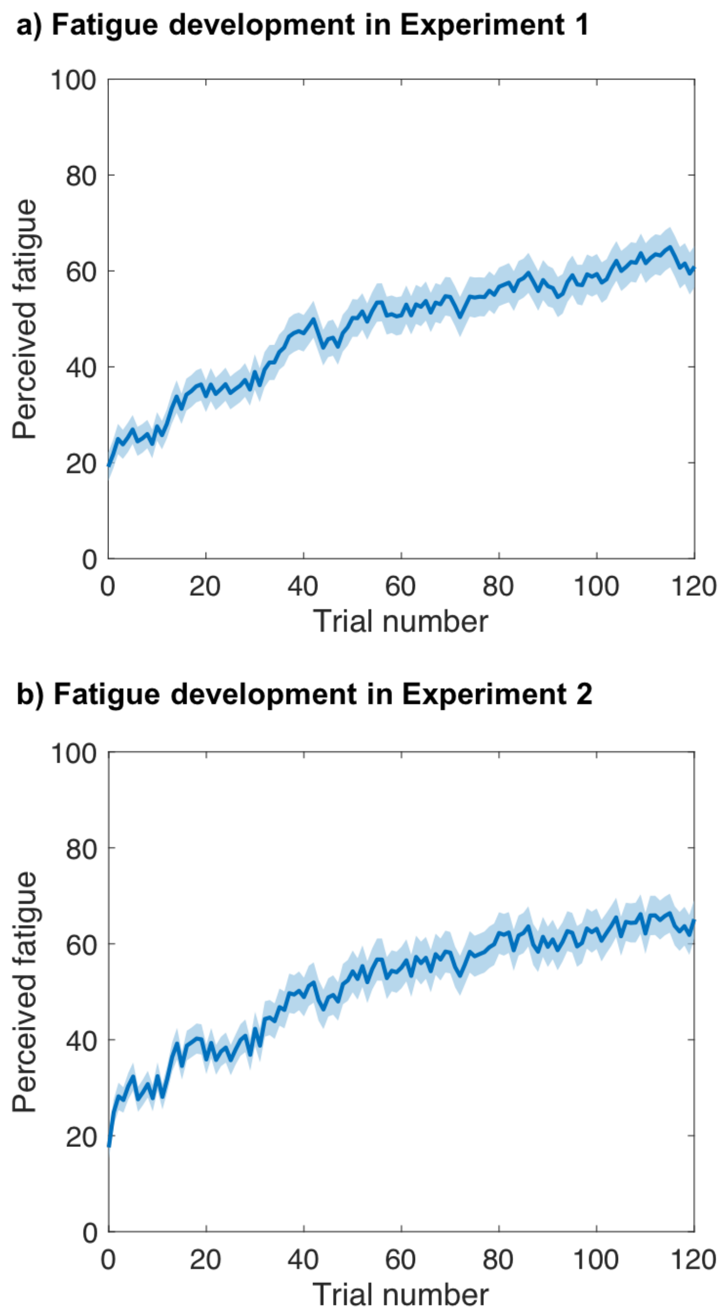

Figure 22. **Perceived fatigue as a function of trial number**. Development of fatigue ratings across the task in (a) Experiment 1 and (b) Experiment 2. Depicted are mean values (lines) including standard errors (shading).

Next, I tested the effects of effort and reward on the change in fatigue from trials *n*-1 to trials *n* in which participants had successfully worked in Experiment 1. Force, reward and the interaction of force and reward as well as trial number were included as predictors in the model, and in addition, a random effect of force and a random effect of subject were fitted. Analyses confirmed that the higher the force, the higher the increase in fatigue, $\chi^2(1) = 27.527$, $p < .001$. In addition, as illustrated in **Figure 23a**, higher obtained rewards were associated with a higher increase in fatigue, $\chi^2(1) = 11.214$, $p < .001$, while the interaction of force and reward was not significant, $\chi^2(1) = 0.759$, $p = .384$. In addition, the change in fatigue decreased over the course of the experiment, $\chi^2(1) = 21.325$, $p < .001$ (**Figure 24a**). Analyses of the rest trials in a separate LMM, with reward and trial number as fixed effects, did not reveal a significant effect of reward on the decrease in fatigue from the current to the previous trial when resting, $\chi^2(1) = 0.943$, $p = .332$, and the effects of rest on fatigue did not significantly change with trial number, $\chi^2(1) = 3.341$, $p = .068$. These results show that in this experiment fatigue changes moment-to-moment, depending on the effort exerted but crucially also on the reward obtained. Higher effort and higher reward both resulted in greater increases in fatigue, yet reward did not affect changes in fatigue during rest.

To test whether higher reward led to increased force production which could possibly account for the effects of reward on fatigue, I ran an additional analysis predicting force by effort level (random effect), reward, the interaction of effort and reward, and trial number, again only including those work trials in which participants had performed the trial successfully. Effort indeed significantly predicted the force exerted, $\chi^2(1) = 3038.907$, $p < .001$, indicating that participants adhered well to the task instructions. While force production overall decreased over the course of the experiment, $\chi^2(1) = 47.736$, $p < .001$ (**Figure 24b**), there was no evidence that higher reward significantly resulted in higher force (reward: $\chi^2(1) = 1.957$, $p = .162$; reward × effort: $\chi^2(1) = 1.730$, $p = .189$; **Figure 23b**).

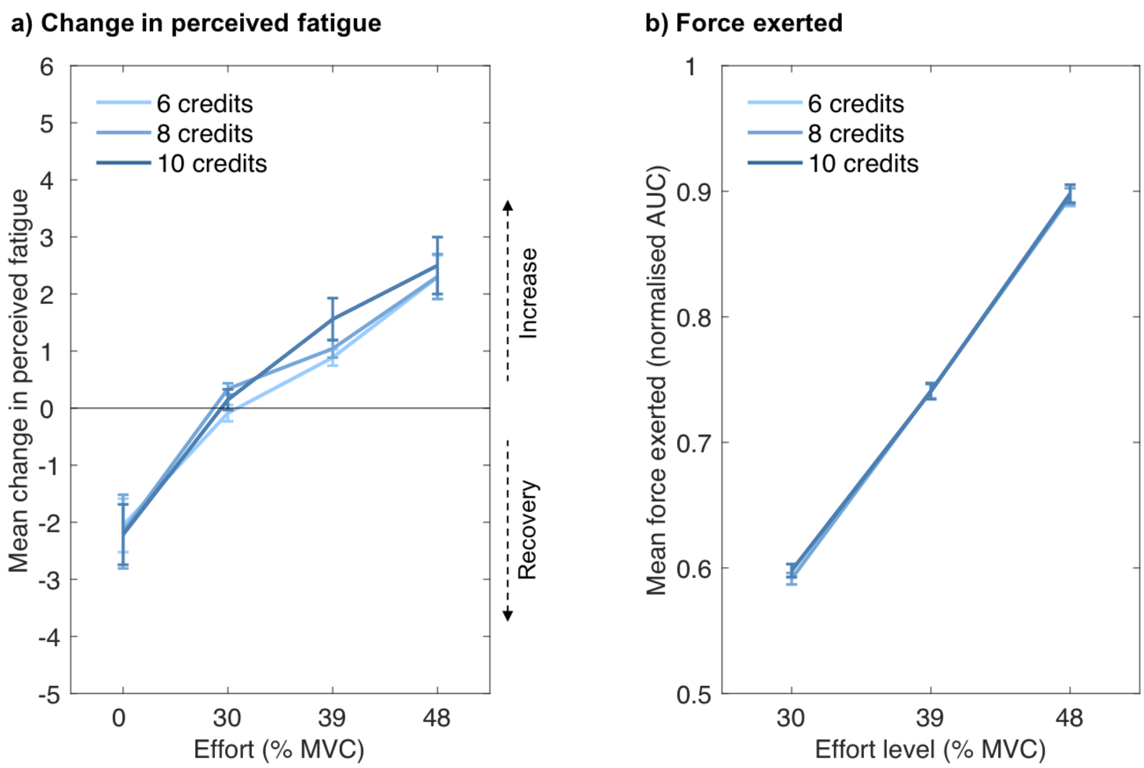

Figure 23**. Effects of effort and reward on perceived fatigue and produced force in Experiment 1. (a)** Mean change in participants' ratings on the question "How tired do you feel?" from trial *n*-1 to trial *n* as a function of rest (0% MVC), effort level and reward (credits earned), showing that perceived fatigue decreases with rest and increases with exertion, in which case higher rewards are associated with slightly higher fatigue increase. **(b)** Mean force exerted on a trial, calculated as the area under the curve (AUC) and normalised for each participant, dependent on effort level and rewards presented on that trial. Only successful trials in which participants exerted the required amount of force and earned the credits associated with that trial were included. Error bars represent standard errors of the means.

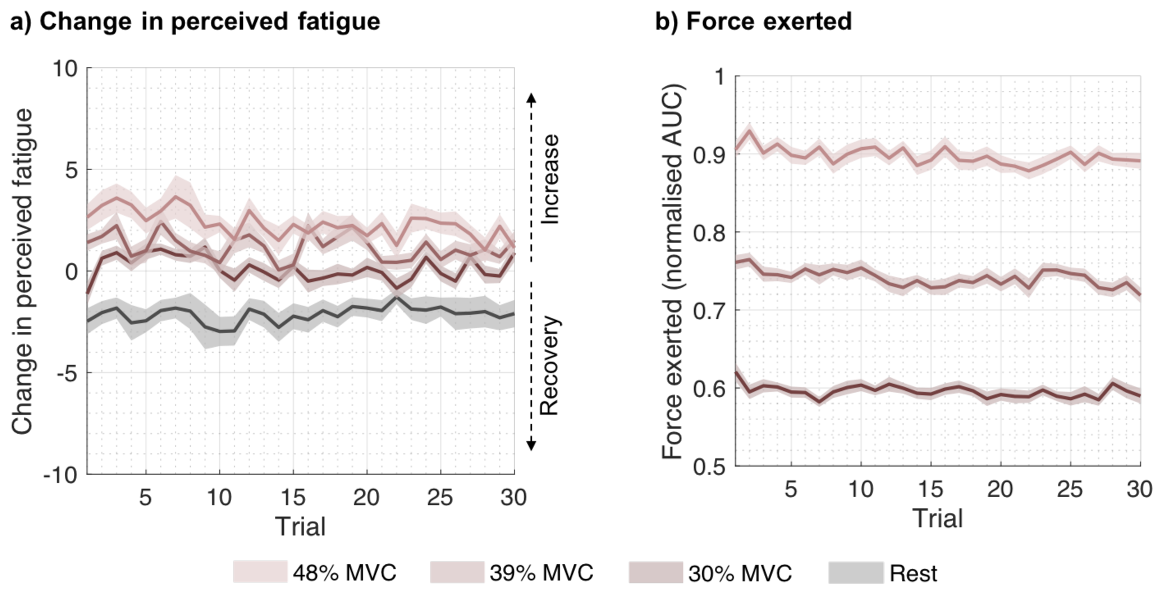

***Figure 24*. Change in perceived fatigue and force exerted in Experiment 1 as a function of effort level and trial number. (a)** Mean change in participants' ratings, including standard errors, on the question "How tired do you feel?" from trial *n*-1 to trial *n* as a function of rest (0% MVC), effort level and the trial in which the respective rest/effort level was required throughout the task. **(b)** Mean force exerted on a trial including standard errors, calculated as the area under the curve (AUC) and normalised for each participant, as a function of effort level and the trial in which the respective effort level was required throughout the task. Only successful trials in which participants exerted the required amount of force and earned the credits associated with that trial were included.

To further test the effects of reward on perceived fatigue, I performed similar analyses to predict fatigue ratings in Experiment 2 in which the reward on each trial was only presented after the force had been produced but before participants rated their fatigue. Therefore, any effect of reward on perceived fatigue would be completely independent of their exerted force, as the incentive for the exertion was only presented after force had been executed. The model included force, reward, the interaction of force and reward as well as trial number as predictors, with a random slope of force. Again, higher force was predictive of higher increases in fatigue, $\chi^2(1) = 10.134$, $p = .001$ (**Figure 25a**), and higher trial number was associated with reduced increases in fatigue, $\chi^2(1) = 16.742$, $p < .001$ (**Figure 25b**). However, the analyses did not reveal an effect of reward on perceived fatigue (reward: $\chi^2(1) = 0.736$, $p = .391$; reward × effort: $\chi^2(1) = 2.621$, $p = .105$). In a separate analysis including rest trials only, reward did not significantly affect recovery, $\chi^2(1) = 0.107$, $p = .744$, but recovery somewhat decreased with trial number, $\chi^2(1) = 16.050$, $p < .001$. Thus, when the amount of reward was completely independent of the force exerted within a trial, moment-to-moment changes in perceived fatigue only depended on the effort exerted.

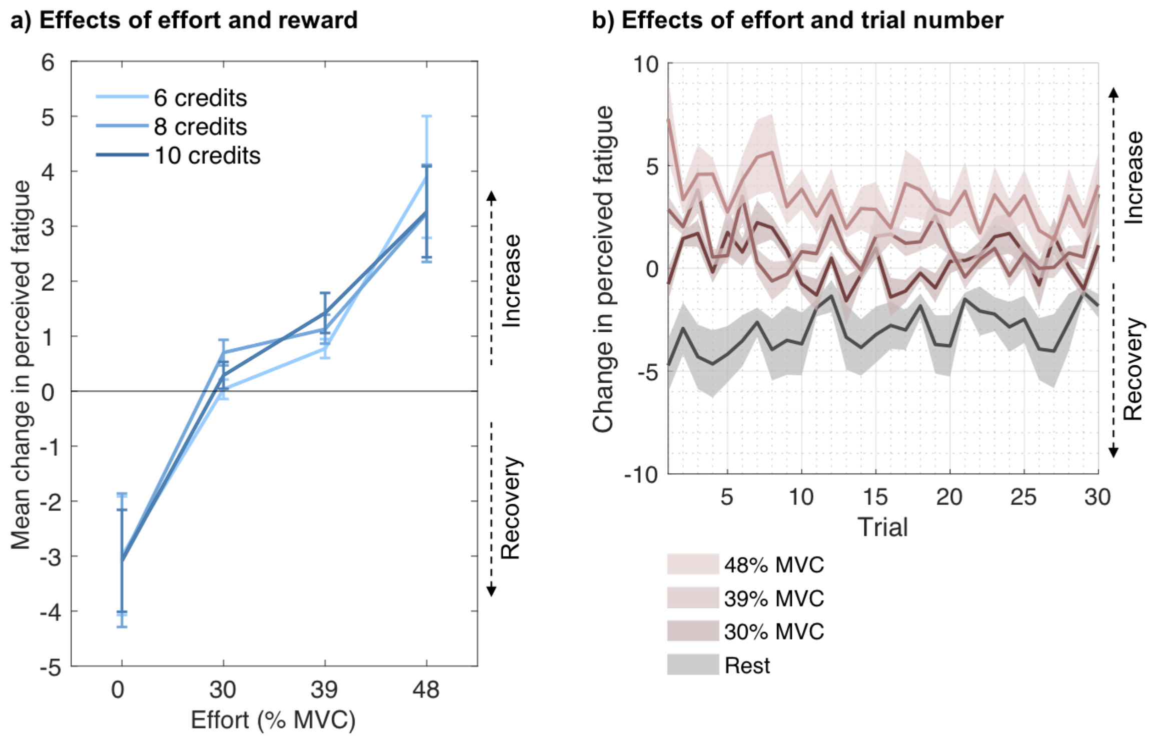

Figure 25. **Change in perceived fatigue in Experiment 2 as a function of effort level, reward and trial number. (a)** Mean change in participants' ratings on the question "How tired do you feel?" from trial n-1 to trial n as a function of rest (0% MVC), effort level and reward (credits earned). **(b)** Mean change in participants' ratings on the question "How tired do you feel?" from trial n-1 to trial n as a function of rest (0% MVC), effort level and the trial in which the respective rest/effort level was required throughout the task. Only successful trials in which participants exerted the required amount of force and earned the credits associated with that trial were included. Error bars and shaded areas represent standard errors of the means.

4.3.1.2 Two components underlie perceived fatigue

To more precisely predict the development of perceived fatigue resulting from repeated exertion, and therefore better understand the effects of working and resting, I used computational modelling and tested whether components similar to the ones identified to underlie fluctuations in motivation following exertion (see **Chapter 2**) would underlie fluctuations in the perception of fatigue.

Five different models were fitted to each participant's ratings and compared using AIC and BIC. Analyses revealed that the Full model, consisting of recoverable and unrecoverable fatigue components, best predicted participants' perceived fatigue in both Experiment 1 and 2 (**Figure 26**). In this model, one parameter quantifies the degree to which a rest leads to recovery and two parameters quantify the degree to which effortful exertion leads to an increase in fatigue.

a) Models tested

Model 1: UF only (no recovery)

$F_{(t)} = F_{start} + UF_{(t-1)} + \theta * E_{(t)}$

Model 2: RF only, one parameter

$F_{(t)} = F_{start} + RF_{(t-1)} + \alpha * E_{(t)} - \alpha * T_{(t)}$

Model 3: RF, one parameter, and UF

$F_{(t)} = F_{start} + (RF_{(t-1)} + \alpha * E_{(t)} - \alpha * T_{(t)}) + (UF_{(t-1)} + \theta * E_{(t)})$

Model 4: RF only, two parameters

$F_{(t)} = F_{start} + RF_{(t-1)} + \alpha * E_{(t)} - \delta * T_{(t)}$

Model 5: Full model

$F_{(t)} = F_{start} + (RF_{(t-1)} + \alpha * E_{(t)} - \delta * T_{(t)}) + (UF_{(t-1)} + \theta * E_{(t)})$

b) Model comparison Experiment 1 **c) Model comparison Experiment 2**

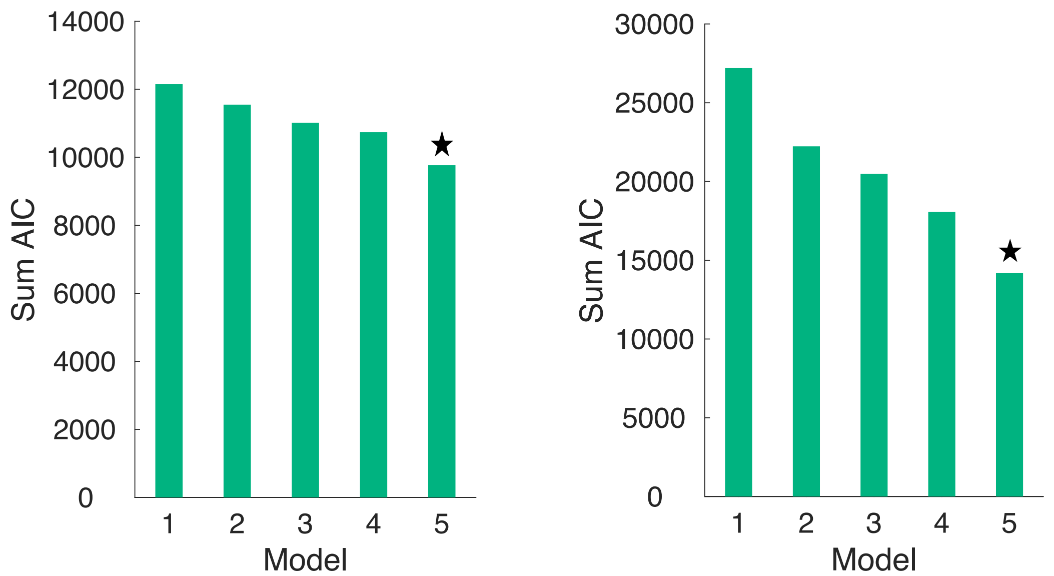

Figure 26. **Modelling perceived fatigue. (a)** List of all models compared. **(b)** Model comparison results for Experiment 1. **(c)** Model comparison results for Experiment 2. The x-axis is depicting the model number and the y-axis the sum of the Akaike Information Criterion (AIC) score, indicating that participants' development of perceived fatigue was best described by the Full model (Model 5) in both experiments, as indicated by the star. Note that additional model comparisons using a Bayesian Information Criterion (BIC) revealed the identical pattern of results. F_{start} = Fatigue rating collected immediately before the first trial of the main task; F = Fatigue on trial t; UF = Unrecoverable fatigue; RF = Recoverable fatigue; E = Force exerted; T = time rested.

4.3.2 Experiment 3

4.3.2.1 Perceived effort primarily depends on current and recent exertion

To test potential effects of force and reward on the perception of effort and whether the perception of effort increased over the course of the task, a mixed effects model with force, reward, their interaction and trial number as predictors including force and subject as random effects was performed on successfully completed work trials. Both force and reward as well as their interaction predicted effort ratings (force: $\chi^2(1) = 482.226$, $p < .001$; reward: $\chi^2(1) = 14.578$, $p < .001$; force × reward: $\chi^2(1) = 4.480$, $p = .034$), revealing that the perception of effort was mainly dependent on the force participants had exerted but that also higher reward was associated with higher perceived effort, especially when the required force was higher (**Figure 27a**). In addition, progression through the experiment (trial number) was associated with a higher perception of effort, $\chi^2(1) = 174.636$, $p < .001$, indicating that participants perception of effort increased over repeated exertion (**Figure 28a**). In a separate LMM including rest trials only, neither reward, $\chi^2(1) = 0.148$, $p = .701$, nor trial number, $\chi^2(1) = 0.188$, $p = .665$, affected effort ratings.

Next, force as a predictor variable was exchanged with effort level in the mixed model in order to assess effects of effort level, reward and trial number on the force successfully exerted in work trials, which was now included as a dependent variable. Force production systematically varied with the effort levels set in the experiment, $\chi^2(1) = 2464.927$, $p < .001$. In addition, higher expected rewards lead to increased force, $\chi^2(1) = 4.751$, $p = .029$, mostly irrespective of the effort level that was required (reward × effort: $\chi^2(1) = 3.505$, $p = .061$; **Figure 27b**). Force also increased over the experiment, $\chi^2(1) = 21.632$, $p < .001$, although **Figure 28b** suggests that trial number only had a small impact on the force exerted. This analysis therefore suggests that the effects of reward on perceived effort described above may (partly) be due to participants exerting more force than required when higher rewards are at stake.

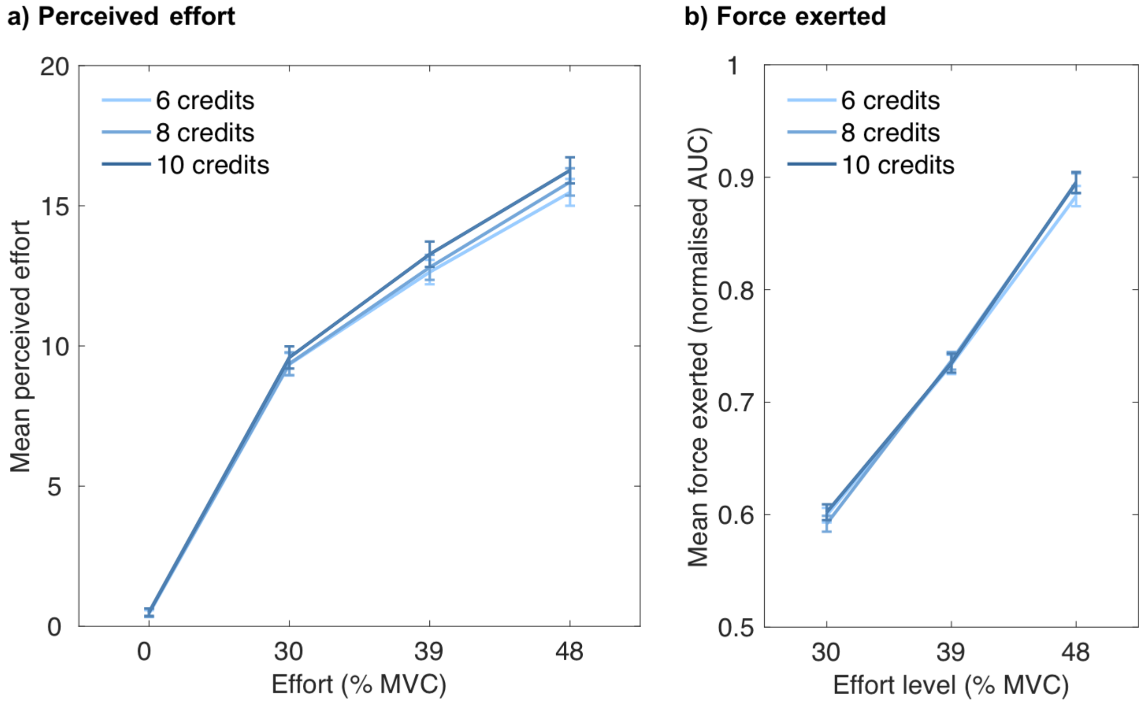

***Figure 27*. Perceived effort and produced force as a function of effort level and reward. (a)** Mean ratings on the question “How hard did you find this?” as a function of rest (0% MVC), effort level and reward (credits earned), showing that the perception of effort increases with exertion and that higher rewards are associated with slightly higher perceived effort. **(b)** Mean force exerted on a trial, calculated as the area under the curve (AUC) and normalised for each participant, dependent on effort level and rewards presented on that trial. Only successful trials in which participants exerted the required amount of force and earned the credits associated with that trial were included. Error bars represent standard errors of the means.

***Figure 28*. Perceived effort and force exerted as a function of effort level and trial number. (a)** Participants' mean ratings, including standard errors, on the question "How hard did you find this" as a function of rest (0% MVC), effort level and the trial in which the respective rest/effort level was required throughout the task. **(b)** Mean force exerted on a trial including standard errors, calculated as the area under the curve (AUC) and normalised for each participant, as a function of effort level and the trial in which the respective effort level was required throughout the task. Only successful trials in which participants exerted the required amount of force and earned the credits associated with that trial were included.

4.4 Discussion

The level of exertion has been proposed as a core determinant of feelings of effort and fatigue during and after physical work, but the precise development over repeated exertion and rests as well as potential effects of rewards have remained unclear. In this study, three experiments were designed to investigate the effects of repeated physical exertion and rest on perceived effort and perceived fatigue. On every trial of these tasks, participants were required to either exert a certain amount of force that varied over trials, by squeezing a hand-held device, or to rest. Afterwards, they rated how tired they felt (Experiments 1 and 2) or how effortful the force was (Experiment 3). Effort level and reward for successful completion of a trial were parametrically and independently varied across the task.

Results provided evidence for the hypothesis that perceived fatigue increases dependent on the degree of effortful exertion and partly decreases with short rest over the course of a task, being susceptible to the same recoverable and unrecoverable components that were found to affect effort-based decisions in Chapter 2. In addition, the perception of effort itself was not only dependent on the force exerted but also increased over the course of the task. Furthermore, the results revealed an association between reward and fatigue in that higher rewards overall lead to higher perceived effort and a somewhat higher increase in fatigue ratings, but only when the rewards that participants could earn on a given trial were presented before they exerted the required level of effort.

The results from the fatigue rating tasks introduced here (Experiments 1 and 2), in which effort was manipulated in a systematic and controlled way, confirm a strong effect of effort on the development of perceived fatigue. They thereby highlight that fatigue is not just a function of, for example, the time spent on a task. However, even though effort and reward were manipulated independently in this experiment, in Experiments 1 and 3 higher rewards here were also predictive of higher subjectively perceived effort and exhaustion even over and above the effort that participants had to exert and even when participants received online visual feedback on their actual force.

How can this relationship between rewards and perceived effort and rewards and perceived fatigue be explained? One possible explanation is that when higher rewards are at stake, people become more motivated and change their behaviour to increase the probability of success but in a way that is more effortful and tiring after all. Recent research has shown that rewards can modulate behaviour, such as a person's vigour or accuracy, even over and above what would be required to obtain the rewards (Manohar et al., 2017; Oudiette et al., 2019; Shadmehr et al., 2019). Notably, as indicated by Experiment 2 and in line with previous work on effort perception in a physical task (Pooresmaeili et al., 2015), such an effect of monetary rewards on perceived fatigue seems to be absent when reward presentation is too dissociated from or noncontingent on behaviour. That is, in the present study there was no evidence for an influence of reward on sensations of fatigue in cases in which the incentive of an action was not known before the action was performed and action invigoration could only be dependent on the required effort. Thus, effects of rewards on perceptions of effort and fatigue must either be a psychological effect of knowing that something is rewarding or must be due to increased vigour, although there was no clear evidence statistically for the latter in this study. These results therefore indicate that effortful exertion has a dominant role in perceived effort and fatigue, while the effects of reward may depend on how information about rewards is presented to participants. As such, they suggest that following physical exertion, a person's perception might primarily be focused on physiological sensations and on internal bodily states. Furthermore, the finding that the same computational model that best predicted changes in motivation over repeated exertion, as discussed in **Chapter 2**, also best predicted changes in the self-reported feeling of fatigue over repeated exertion suggests a close relationship between fluctuations in perceived fatigue and fluctuations in motivation.

In addition, the results of Experiment 3 suggested that the perception of effort itself increases over repeated exertion. This finding supports and extends previous research that showed an increase in the feeling of effort with time spent on a cognitive task (Bijleveld, 2018) and with studies which suggested that the subjective perception of exertion and its increase throughout a continuous cycling exercise are a crucial determinant for people stopping their current actions (Crewe et al., 2008; Marcora and Staiano, 2010), as well as with very early studies which found that sustained isometric force production lead to an altered perception of effort (Cain and Stevens, 1971; Jones and Hunter, 1983; Stevens and Cain, 1970). A current account on fatigue in stroke patients suggests that fatigued patients show a heightened perception of effort which is due to an inability of top-down corollary discharge signals to suppress signals from sensorimotor regions (Kuppuswamy, 2017). The results of the present study might suggest that these discharge signals gradually weaken over repeated exertion, leading to an increased perception of effort and eventually to an increased perception of fatigue. They thereby provide support for the proposal that fatigue is associated with an increase of the costs associated with an action, and perhaps, at least in the case of physical exertion, typically constitutes an adaptive mechanism that ultimately prevents complete exhaustion and maintains homeostasis when behaviour is adjusted accordingly (Noakes, 2012).

Lastly, linear mixed effects models indicated that the effects of effort (and potentially rest) on ratings of fatigue might slightly decrease over the course of the task. While sensations of fatigue might possibly be subject to respective further dynamics, and when people become more and more fatigued, their perception of and differentiation between small differences in fatigue may possibly decrease, there could also be several other reasons for this finding which are rather inherent to the task and the respective assessment of perceived fatigue. First, it could be the case that some participants somewhat overestimated changes in their fatigue at the beginning of the task. Evidence for this assumption is provided by the fact that some participants reached a ceiling, i.e. rated themselves as completely exhausted before the end of the task while still being able to work. Second, this pattern may be partly explained by changes in motivation and resulting subtle changes in behaviour, supported by the finding that participants tended to overall put in somewhat less force with progression through the task. Future work could try to disentangle these effects more closely.

4.5 Conclusion

This study showed that the perception of fatigue resulting from repeated physical exertion is mainly driven by the effort exerted and the rest taken, and it seems closely linked with an altered perception of effort. It also demonstrated that perceived fatigue fluctuates on a moment-to-moment basis, depending on a recoverable and an unrecoverable fatigue component, and thereby – together with the study described in Chapter 2 – suggests that the conscious perception of fatigue and the willingness to exert effort are underpinned by similar or related factors, highlighting the close link between the effects of effortful exertion on perceived fatigue and on motivation. In future research, the three parameters identified to capture individual effects of exertion and rest on fatigue development may allow us to precisely specify and quantify potential abnormalities in diverse patient populations as well as respective effects of treatment. In addition, using both the effort rating and the fatigue rating tasks in those populations might have the potential to shed new light on the difference and interplay between abnormal perception of effort, abnormal perception of fatigue and their effects on behaviour, which might be overlooked in standard questionnaire assessments.

5 Effects of dopamine on fatigue development in Parkinson's disease

5.1 Introduction

In healthy people, fatigue classically arises through effortful exertion and declines through rest (Boksem and Tops, 2008; Carroll et al., 2017; Hockey, 2011; Meyniel et al., 2014; Tanaka and Watanabe, 2012). In some cases, however, the feelings of exhaustion seem to persist. While persistent fatigue is also commonly reported in otherwise healthy people, it is present in more severe forms in various neurological, psychiatric and other medical conditions (Chaudhuri and Behan, 2004; Cullen et al., 2002; Demyttenaere et al., 2005; Lerdal et al., 2009, 2007; Skapinakis et al., 2003). One neurological condition that is typically associated with an altered experience of fatigue is Parkinson's disease (PD). Over 50% of these patients tend to report abnormal fatigue that affects their daily life, even in very early stages of the disease (Friedman et al., 2016; Herlofson and Larsen, 2002). Yet, it is highly unclear which, if any, treatments are effective (Elbers et al., 2015; Franssen et al., 2014).

How do these heightened levels of fatigue arise? Mechanistic accounts have been limited, but some have highlighted that the degeneration of midbrain dopaminergic nuclei, as is typical in PD, may be associated with fatigue in these patients and suggested that, compared to healthy people, they may be impaired to recover during periods of rest (Chaudhuri and Behan, 2004, 2000; Friedman et al., 2007). While dopaminergic medication is often given to ameliorate PD patients' motor symptoms by impacting their dopamine deficiency, certain types of dopaminergic medication are sometimes also given as a treatment of fatigue in PD as well as in some other disorders (Kalia and Lang, 2015; Lou, 2009; Schifitto et al., 2008; Stahl, 2002).

Highlighting a link between dopamine and effort, recent research in monkeys suggested that dopaminergic neurons from the substantia nigra pars compacta in the midbrain encoded not only the expected reward but also the anticipated effort cost of an option (Varazzani et al., 2015). Work in rodents, too, supports the idea that dopamine levels in the striatum are specifically related to the avoidance of options involving high physical effort (Salamone et al., 2007) and to the predicted cost of repeatedly performing an action (Filla et al., 2018) and that these dopamine levels may be impacted by recent exertion (Iodice et al., 2017b).

Moreover, recent studies in PD patients have shown that dopaminergic medication modulates their willingness to exert physical effort (Chong et al., 2015; Le Bouc et al., 2016; Le Heron et al., 2018b) as well as cognitive effort (McGuigan et al., 2019) for monetary rewards, probably by altering activity in the midbrain and connected frontal regions that guide effort-based decisions (Cools, 2015; Kurniawan et al., 2011; Le Heron et al., 2018a; Salamone et al., 2016; Westbrook and Braver, 2016; Westbrook and Frank, 2018). On the other hand, dopamine levels in PD have also been associated with reward sensitivity (Muhammed et al., 2016) and thus it is possible that fatigue might, in some way, be related to reward rather than effort processing.

Yet, although there have been several lines of research suggesting effects of dopamine on motivation and on the processing of effort and reward, its relationship to fatigue is not well understood. To date, although studies directly linking dopamine with effort processing have investigated motivation, they have not systematically examined the effect of dopamine on sensations of fatigue. It therefore remains unclear if dopamine changes sensations of fatigue on a moment-to-moment basis or whether it is only involved in increasing motivation which may in turn affect fatigue. In addition, it is unclear whether PD patients tend to experience heightened levels of fatigue because they get more fatigued by exerting effort, i.e. small exertions cause high fatigue, or whether once they are fatigued following exertion they cannot recover as quickly during periods of rest. Nor is it clear how this changes as a function of dopamine availability.

Here, by varying required effort levels, reward levels and periods of rest independently from each other on a trial-by-trial basis and asking participants to rate their current feeling of fatigue on every trial, I was able to specifically test the hypotheses that dopamine might impact on the development of subjective feelings of fatigue and may alter the effects of effort, reward and rest on changes in perceived fatigue in PD patients. For this purpose, I used the fatigue rating task and the analysis approach described in **Chapter 4** (Experiment 1) and tested PD patients in dopamine depleted and medicated states on two separate days.

5.2 Methods

5.2.1 Participants

Thirty patients with a clinical diagnosis of idiopathic Parkinson's disease and with no history of other neurological or psychiatric illnesses were included in the study. They were recruited from clinics in the Oxfordshire area. Participants were informed that they would be paid according to performance in this task. In reality, they were paid as part of a larger payment of typically £45 to compensate for their time spent on this and a subsequent experiment and to cover travel expenses. The study was approved by the local ethics committee and written consent was obtained from all participants in accordance with the Declaration of Helsinki.

All patients were currently established on levodopa therapy. They were tested in two counterbalanced sessions, one week apart, in the mornings. In one session they had taken their dopaminergic medication as normal (ON), while in the other session they had withheld it since the night before (OFF).

One participant was excluded from the analyses because the participant had taken an adjunctive dopaminergic medication (a monoamine oxidase inhibitor) in the OFF session, and another was excluded because of an overall failure to successfully complete the highest effort level trials (success rate < 25% on those trials). The resulting sample of N = 28 patients (5 females) had a mean age of 68.64 years (SD = 6.69; range 46-84). In addition to their levodopa therapy, some of these patients took a concomitant dopamine agonist (n = 9) or were on other adjunctive therapies (monoamine oxidase inhibitor: n = 9; Amantadine: n = 2). Further details are provided in **Table 4**. Statistical analysis confirmed that the time since the last dose of dopaminergic medication differed significantly between the ON and the OFF condition, $Z = 4.623$, $p < .001$.

5.2.2 Questionnaires

In addition to the main task participants were asked to complete, a collection of questionnaires was administered. The severity of Parkinson's disease was assessed using the Unified Parkinson's Disease Rating Scale (UPDRS; Goetz et al., 2008) total score and Hoehn and Yahr stage. The UPDRS-III (motor score) was repeated in the ON and OFF states. The Addenbrooke's cognitive examination version III (ACE-III), which has been shown to be sensitive to cognitive impairment in several neurodegenerative diseases, was administered to examine cognitive ability (Hsieh et al., 2013), and patients were screened for depression with the Geriatric Depression Scale (GDS), a short screening tool used across a range of disorders but also in the otherwise healthy population, especially in the elderly (Sheikh and Yesavage, 1986). Scores on the GDS between 0 and 15 indicate the level of depression. In addition, they were tested for clinical apathy using the Lille Apathy Rating Scale (LARS), a semi-structured clinical interview which has been validated in Parkinson's disease (Sockeel et al., 2006), with scores ranging from -36 to +36. Fatigue was assessed using the Fatigue Severity Scale (FSS; Krupp et al., 1989). This is a nine-item questionnaire assessing the degree to which someone has been impacted by fatigue over the past week by providing one score between 1 and 7. It has been validated and administered across populations and disorders, among them Parkinson's disease (Herlofson and Larsen, 2002). Scores for the final sample in this study are presented in **Table 4**. Note that two of the patients had a relatively low score on the ACE, but it was made sure that they had understood the task.

Table 4

Medical information and questionnaire scores

	Mean (SD)
Levodopa equivalent dose (mg/24h)	603.81 (347.91)
Time since last dose ON (hours)	3.86 (2.61)
Time since last dose OFF (hours)	16.33 (3.77)
UPDRS total	59.26 (21.30)
Hoehn and Yahr Stage	2.18 (0.71)
UPDRS-III ON	42.43 (14.30)
UPDRS-III OFF	48.21 (12.79)
Global cognition (ACE)	92.29 (8.10)
Depression (GDS)[1]	2.22 (2.05)
Apathy (LARS)	-24.82 (6.57)
Fatigue (FSS)	3.44 (1.06)

Note. UPDRS = Unified Parkinson's Disease Rating Scale; ACE = Addenbrooke's Cognitive Examination; GDS = Geriatric Depression Scale; LARS = Lille Apathy Rating Scale; FSS = Fatigue Severity Scale; [1]Data was missing from one patient.

5.2.3 Apparatus, experimental design and procedure

Apparatus as well as experimental design and procedure (**Figure 29**) were identical to Experiment 1 described in **Chapter 4**.

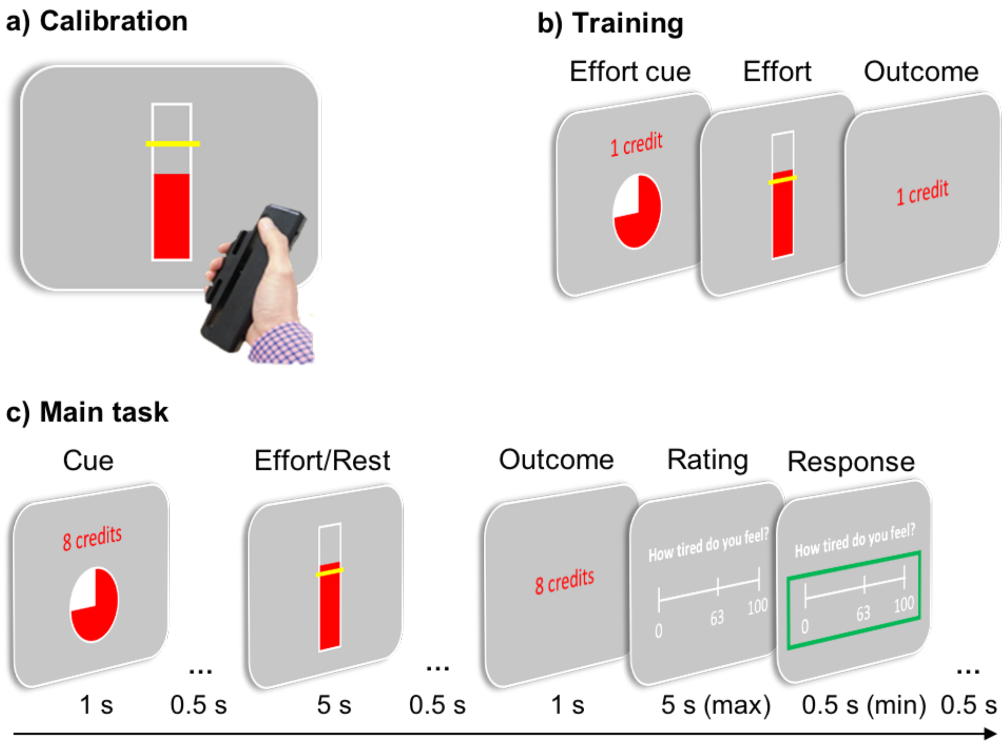

Figure 29. **Illustration of the different parts of the experiment. (a)** Each participant's maximum voluntary contraction (MVC) was obtained by asking them to exert as much grip force as possible on a handheld dynamometer while receiving real-time visual feedback. **(b)** Participants were trained to reach four levels of effort which were set depending on their individually calibrated MVC (0, 30, 39, and 48% of each participant's MVC). On each trial, a cue first indicated the effort that participants subsequently had to exert. **(c)** Trial outline for the Main task. Participants were presented with a cue indicating how much effort they had to exert (rest or one of three possible effort levels) and the rewards they could earn on that trial (6, 8, or 10 credits). They then either had to rest or to squeeze above the required effort level (i.e. the required proportion of each participant's previously determined MVC) using a handheld dynamometer for a minimum of 3 seconds in order to receive the credits. For this purpose, participants were presented with a vertical bar, providing them with real-time feedback on their force (red filling) and indicating the target level by a yellow line superimposed on the bar. Subsequently, they received feedback on the credits earned on that trial and were then asked to rate on a visual analogue scale ranging from 0 to 100 how tired they are feeling. All stimuli were presented on a black background.

Here, the effort levels were calibrated to each participant's maximum voluntary contraction (MVC) separately for the ON and the OFF condition. This ensured that subjective effort was comparable across conditions and that participants were able to complete the task even when being OFF dopaminergic medication. Crucially, their MVCs did not differ significantly between ON and OFF conditions, $t(26) = 1.055$, two-tailed $p = .301$ [5], allowing for direct comparison of fatigue ratings ON versus OFF medication.

5.2.4 Statistical analysis

First, changes in participants' fatigue ratings from trial *n*-1 to trial *n* as well as their behaviour (force produced) on trial *n* were analysed with linear mixed-effects models (LMM) using the lmer function from the lme4 package (Bates et al., 2015b) in R 3.5.2 (R Core Team, 2018) with the maximum likelihood estimation method. Force on each trial was calculated as the area under the curve of the voluntary contraction trace recorded from the dynamometer, using the *trapz* function in Matlab. For every participant, the area under the curve on any given trial was normalised by the maximum value calculated for this participant to account for interindividual differences in force exerted.

Trials *n* in which participants worked and trials *n* in which they rested were examined in separate LMMs. This was based on the assumption that changes in fatigue would be (linearly) scaled by the amount of force when they exerted force,

[5] Note that for one participant, settings affecting MVC values were changed between the ON and the OFF condition. Therefore, the respective participant was excluded from this analysis.

while taking rests might have a differential impact on changes in fatigue, as also indicated by the results of Chapters 2 and 4. Only trials *n* in which participants had successfully squeezed and thus obtained the credits were included in the model that was aimed at examining work trials. This resulted in the exclusion of $M = 6.10\%$ ($SD = 9.48$) trials in the ON condition and $M = 3.90\%$ ($SD = 5.99$) trials in the OFF condition, while overall the percentage of trials excluded did not significantly differ between conditions, $Z = 1.738$, $p = .082$. In all models, a subject-level random intercept, which allowed modelling of potential variability between participants, was included.

In all analyses of work trials, a random slope for force (or effort level) was additionally included, similar to the analyses described for the healthy young sample in **Chapter 4**. Trial number and session (first or second) and their interaction with medication (ON or OFF) were added as additional predictors to account for potential confounds, such as a potential reduction in force or in the manipulation of the rating scale over the course of the task e.g. in cases in which participants had reached the upper limit of the rating scale before the end of the experiment, or a potential reduction in force or a change in the use of the rating scale in the second compared to the first session. The inclusion (and exclusion) of predictors, interactions and additional random slopes was chosen to assure a good balance between model interpretability, predictive accuracy and model complexity (Bates et al., 2015a; Matuschek et al., 2017). Force, effort, reward and trial number were coded as continuous variables. Effects were tested for statistical significance using a Type II Wald chi-square test, i.e. χ^2 and *p*-values refer to comparisons between the tested model and the same model without the respective main effect or interaction of interest.

5.2.5 Computational modelling

The same computational model and modelling procedure as described for Experiment 1, **Chapter 4**, was used.

5.3 Results

5.3.1 Dopaminergic medication affects perceived fatigue

As a first analysis, I was interested in testing whether PD patients ON dopaminergic medication developed less fatigue during the task than the same patients when being unmedicated. Before the first trial of the main task, participants initially rated on a visual analogue scale, which ranged from 0 to 100, how tired they currently felt (baseline rating; trial 0). There was no significant difference in fatigue ratings between the ON and the OFF condition before the start of the task, $Z = 0.868$, two-tailed $p = .386$. In both conditions, fatigue ratings on the visual analogue scale increased over the course of the task (**Figure 30**). Notably, during the course of the task PD patients OFF dopaminergic medication tended to report higher levels of fatigue than ON dopaminergic medication, differing significantly from one another both in the middle, $Z = 2.518$, one-tailed $p = .006$ (trial 60), and at the end of the task, $Z = 1.911$, one-tailed $p = .028$ (trial 120).

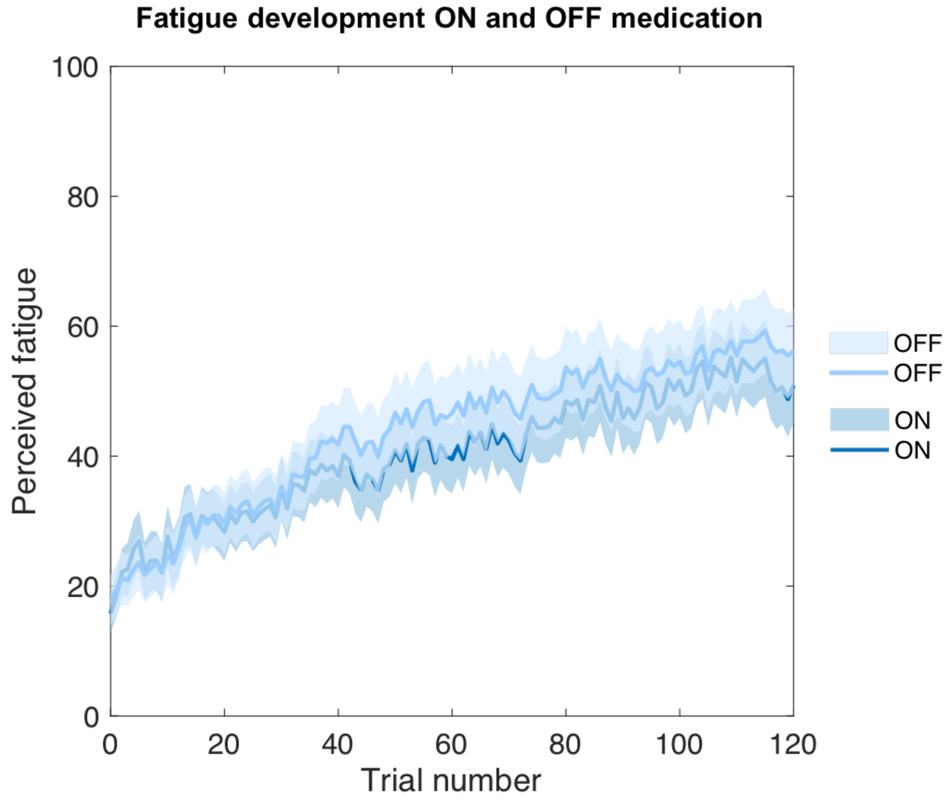

Figure 30. **Perceived fatigue as a function of trial number**. Development of fatigue ratings across the task in Parkinson's disease patients when they had taken their dopaminergic medication as normal (ON) and when they had withheld it since the night before (OFF). Depicted are mean values (lines) including standard errors (shading).

5.3.2 Dopaminergic medication improves recovery during rests

In line with the findings from the healthy young sample described in Chapter 4, PD patients' fatigue improved during short periods of rest. This recovery effect was more pronounced in the ON condition (**Figure 31**). To more precisely investigate how dopaminergic medication may alter fatigue in PD patients, I tested its effects on fatigue decrease from trials n-1 to trials n in which participants had rested using a linear mixed effects model. Medication, reward, trial number and session as well as interactions of medication and the other three predictors were included as fixed effects in the model, and in addition, a random effect of subject was fitted. The analyses revealed that recovery was increased in patients ON compared to OFF medication, $\chi^2(1) = 10.187$, $p = .001$, as depicted in **Figure 31**.

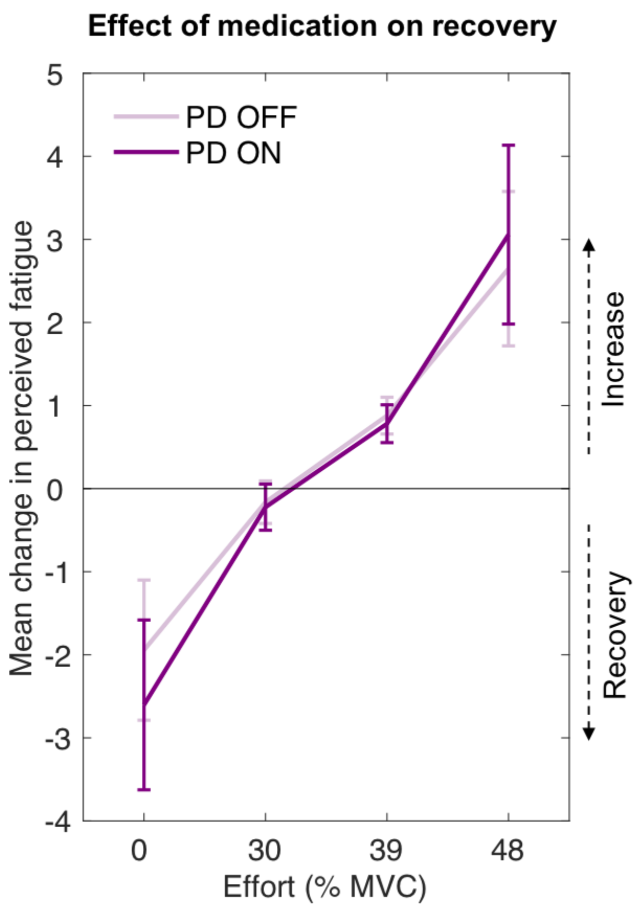

***Figure 31*. Effects of medication and rest/effort on perceived fatigue.** (a) Mean change in participants' ratings on the question "How tired do you feel?" from trial *n*-1 to trial *n* as a function of rest (0% MVC) and effort level, separately for Parkinson's disease patients when ON and when OFF dopaminergic medication. This in particular illustrates that dopamine levels in PD patients affect recovery during rest. Only successful trials in which participants exerted the required amount of force and earned the credits associated with that trial were included. Error bars represent standard errors of the means.

Reward did not significantly affect recovery, $\chi^2(1) = 0.049$, $p = .826$, and recovery was not found to change with progression through the task, $\chi^2(1) = 0.088$, $p = .767$ (**Figures 32** and **33**), indicating that the rate of recovery remained constant across time regardless of the patients' current level of fatigue. However, there was a significant effect of session in that rests had less of a restorative effect in the second compared to the first session, $\chi^2(1) = 19.273$, $p < .001$, but none of the interactions were significant (medication × reward: $\chi^2(1) = 0.433$, $p = .511$; medication × trial number: $\chi^2(1) = 0.090$, $p = .764$; medication × session: $\chi^2(1) = 0.095$, $p = .758$). Thus, the fact that there was no significant interaction between medication and session suggests that the effect of dopaminergic medication on recovery cannot be explained by the session effect.

5.3.3 Dopaminergic medication slightly alters effects of rewards and effort

Next, in order to investigate whether dopamine levels alter the effects of effort and possibly of reward on perceived fatigue, I analysed changes in fatigue ratings from trials n in which participants had successfully worked to trials n-1. Medication, force, reward, trial number and session as well as interactions of medication and the other four predictors and a medication × force × reward interaction were included as fixed effects in the model. Random effects of force and subject were fitted. Analyses confirmed that the higher the force, the higher the increase in fatigue, $\chi^2(1) = 6.235$, $p = .013$ (**Figure 32**). There was no significant main effect of medication, $\chi^2(1) = 0.851$, $p = .356$, or reward, $\chi^2(1) = 2.799$, $p = .094$. Yet, there was a (borderline) significant interaction of medication, force and rewards, $\chi^2(1) = 3.960$, $p = .047$, likely driven by a somewhat higher sensitivity to efforts in medicated patients in particular when low reward was at stake (**Figure 32**).

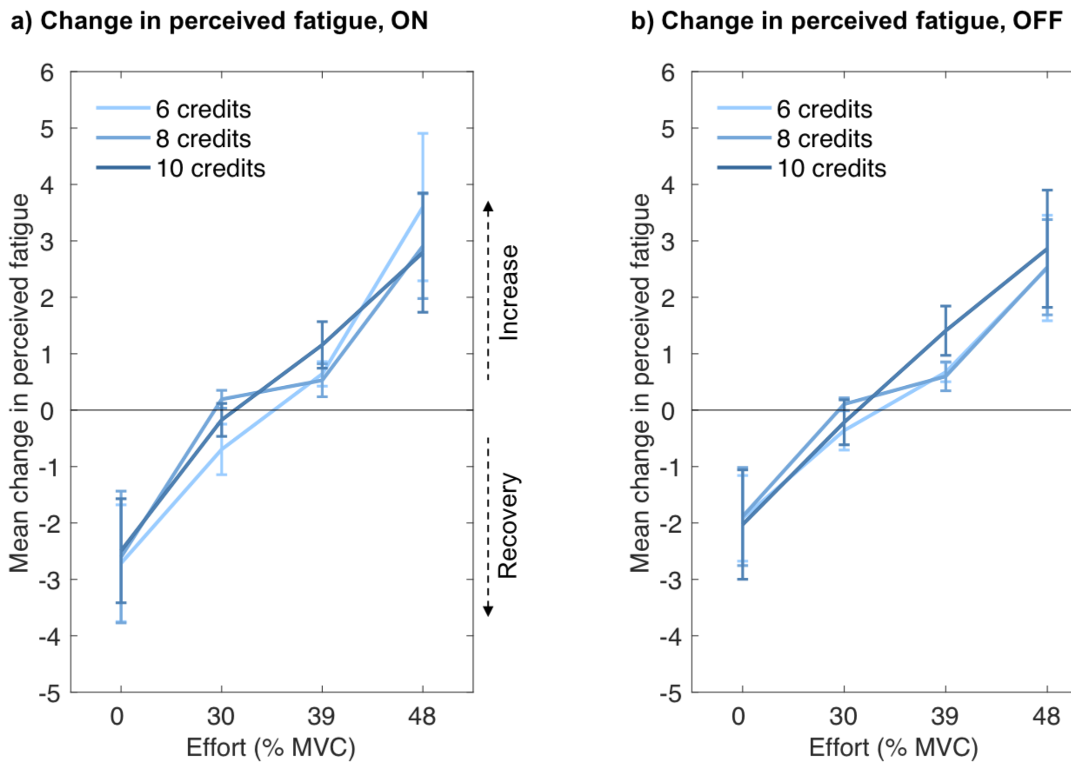

***Figure 32*. Effects of medication, effort and reward on perceived fatigue.** Mean change in participants' ratings on the question "How tired do you feel?" from trial *n*-1 to trial *n* as a function of rest (0% MVC), effort level and reward (credits earned), separately for Parkinson's disease patients when (a) ON dopaminergic medication and when (b) OFF dopaminergic medication. Only successful trials in which participants exerted the required amount of force and earned the credits associated with that trial were included. Error bars represent standard errors of the means.

All of the other interactions tested did not significantly predict changes in fatigue from the previous to the current trial, all $\chi^2(1) < 1.412$, $p > .234$. However, the changes in participants' fatigue ratings were smaller in the second as compared to the first session, $\chi^2(1) = 8.908$, $p = .003$, and slightly decreased with trial number, $\chi^2(1) = 3.995$, $p = .046$ (**Figure 33**). Results were similar when the four-way interaction of medication, force, reward and session was included in the model, with the exception of a significant force × session interaction, $\chi^2(1) = 11.895$, $p <$

.001, indicating that the above reported effects of medication could not be explained by session effects.

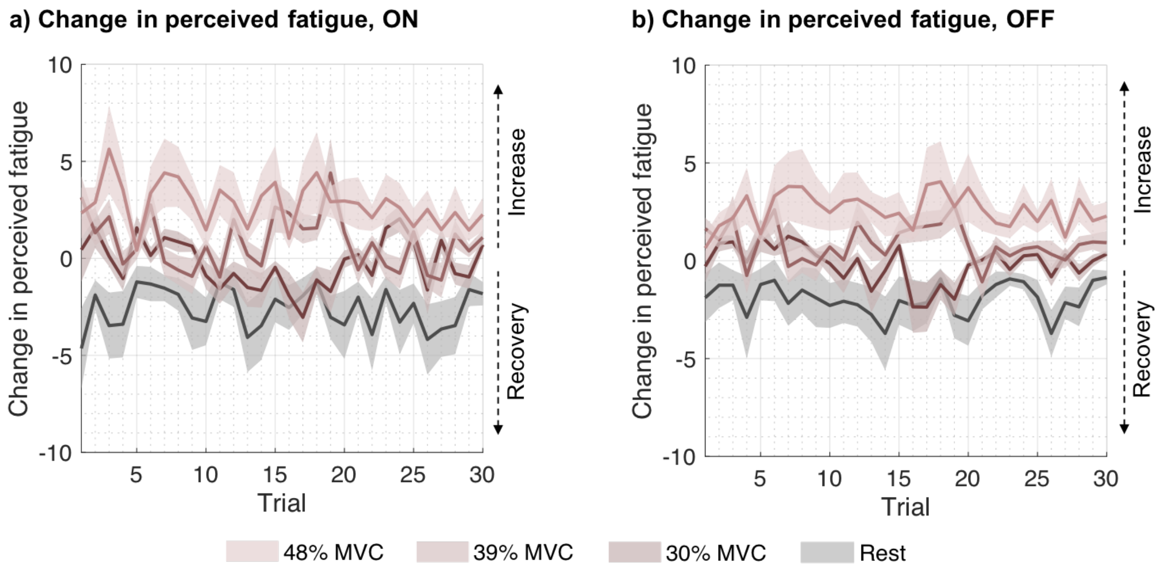

Figure 33**. Change in perceived fatigue as a function of medication, effort and trial number.** Mean change in participants' ratings, including standard errors, on the question "How tired do you feel?" from trial *n*-1 to trial *n* as a function of rest (0% MVC), effort level and the trial in which the respective rest/effort level was required throughout the task, separately for Parkinson's disease patients when (a) ON dopaminergic medication and when (b) OFF dopaminergic medication. Only successful trials in which participants exerted the required amount of force and earned the credits associated with that trial were included.

To test whether having taken dopaminergic medication or whether having been offered higher rewards had potentially led to an increase in participants' force production which may partly account for or have biased the observed effects, I ran an additional analysis predicting force by effort level (random effect), medication, reward, trial number and session as well as interactions of medication and the other four predictors and a medication × effort × reward interaction, again only including those trials in which participants had performed the trial successfully. As expected, the effort level significantly predicted the force exerted, $\chi^2(1) = 445.484$, $p < .001$, indicating that participants adhered well to the task instructions (**Figure 34**). In addition, higher expected reward increased the force that participants exerted, $\chi^2(1) = 5.004$, $p = .025$, and when ON medication patients exerted more force during the experiment than when they had withdrawn from their medication, $\chi^2(1) = 9.328$, $p = .002$, although **Figure 34** suggests that these effects were relatively small.

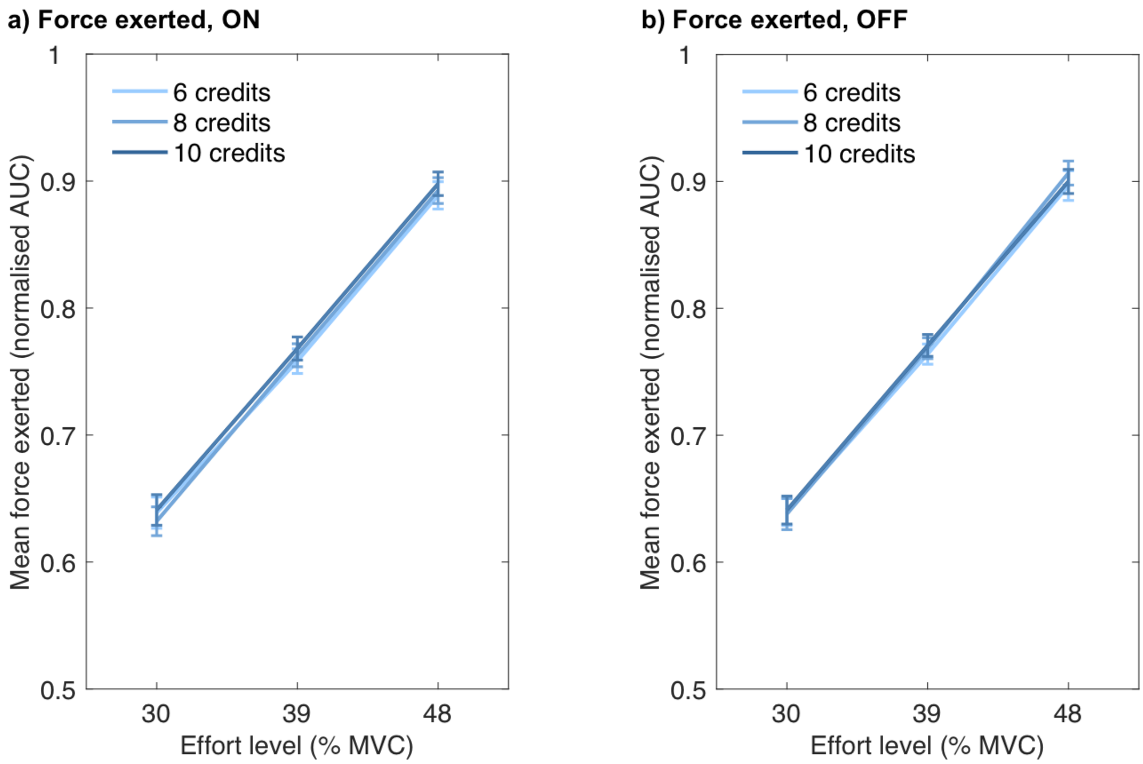

***Figure 34*. Effects of medication, effort and reward on produced force.** Mean force exerted on a trial, calculated as the area under the curve (AUC) and normalised for each participant, dependent on effort level and rewards presented on that trial, separately for Parkinson's disease patients when (a) ON dopaminergic medication and when (b) OFF dopaminergic medication. Only successful trials in which participants exerted the required amount of force and earned the credits associated with that trial were included. Error bars represent standard errors of the means.

In addition, force production overall slightly decreased over the course of the experiment, $\chi^2(1) = 7.999$, $p = .005$, as indicated in **Figure 35**, and was overall higher in the second as compared to the first session, $\chi^2(1) = 101.287$, $p < .001$. However, none of the interactions approached significance, all $\chi^2(1) < 2.118$, $p >$ .145. Results were similar when the four-way interaction of medication, force, reward and session was included in the model.

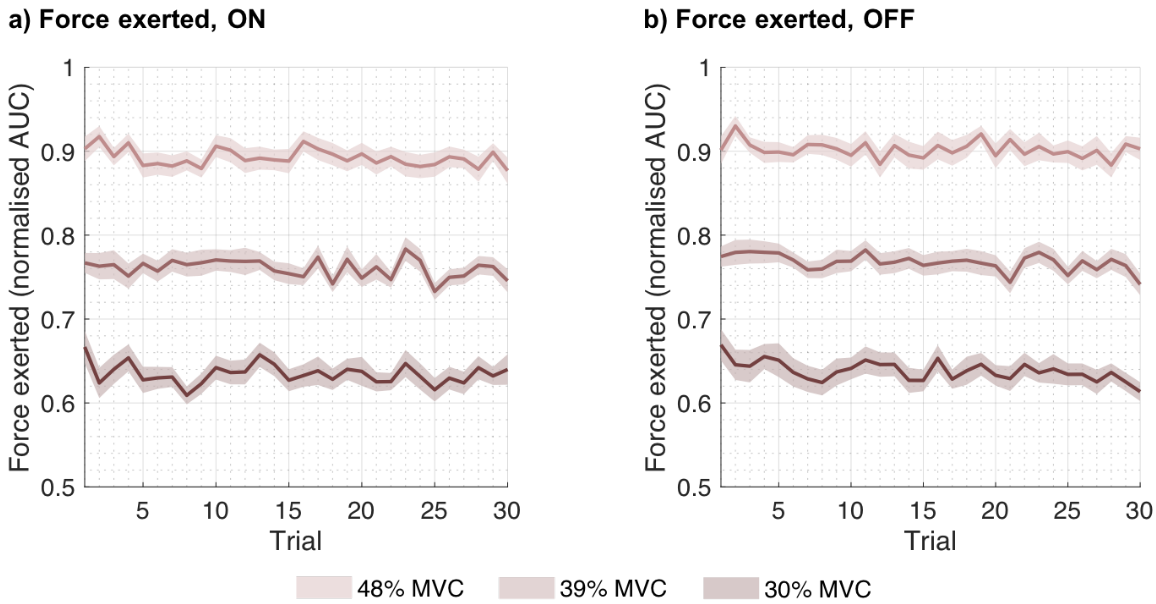

***Figure 35*. Force exerted as a function of medication, effort level and trial number.** Mean force exerted on a trial including standard errors, calculated as the area under the curve (AUC) and normalised for each participant, as a function of effort level and the trial in which the respective effort level was required throughout the task, separately for Parkinson's disease patients when (a) ON dopaminergic medication and when (b) OFF dopaminergic medication. Only successful trials in which participants exerted the required amount of force and earned the credits associated with that trial were included.

5.3.4 Fatigue model quantifies effects of dopamine on short-term recovery

To support the analyses outlined above and to more precisely predict the development of perceived fatigue in PD patients ON and OFF dopaminergic medication and therefore better understand the effects of dopamine on perceived fatigue, more sophisticated computational modelling procedures were additionally used. In particular, I was interested in testing whether the computational model introduced in **Chapter 4** would be able to capture and specify the effects of dopamine on the subjective perception of fatigue.

Five different models were fitted for each participant's ratings and compared using AIC and BIC as described in Chapter 4. Analyses revealed that the Full model, consisting of recoverable and unrecoverable fatigue components, best predicted participants' perceived fatigue both ON and OFF dopamine (**Figure 36**). In this model, one parameter quantifies the degree to which a short rest leads to recovery and two parameters quantify the degree to which effortful exertion leads to an increase in fatigue. The fact that fatigue ratings both in the ON and in the OFF condition could best be described by the full model demonstrates that the development of perceived fatigue follows a similar pattern in both cases and therefore allowed for the direct comparison of model parameters between conditions.

a) Models tested

Model 1: UF only (no recovery)
$F_{(t)} = UF_{(t-1)} + \theta * E_{(t)}$

Model 2: RF only, one parameter
$F_{(t)} = RF_{(t-1)} + \alpha * E_{(t)} - \alpha * T_{(t)}$

Model 3: RF, one parameter, and UF
$F_{(t)} = (RF_{(t-1)} + \alpha * E_{(t)} - \alpha * T_{(t)}) + (UF_{(t-1)} + \theta * E_{(t)})$

Model 4: RF only, two parameters
$F_{(t)} = RF_{(t-1)} + \alpha * E_{(t)} - \delta * T_{(t)}$

Model 5: Full model
$F_{(t)} = (RF_{(t-1)} + \alpha * E_{(t)} - \delta * T_{(t)}) + (UF_{(t-1)} + \theta * E_{(t)})$

b) Model comparison, ON **c) Model comparison, OFF**

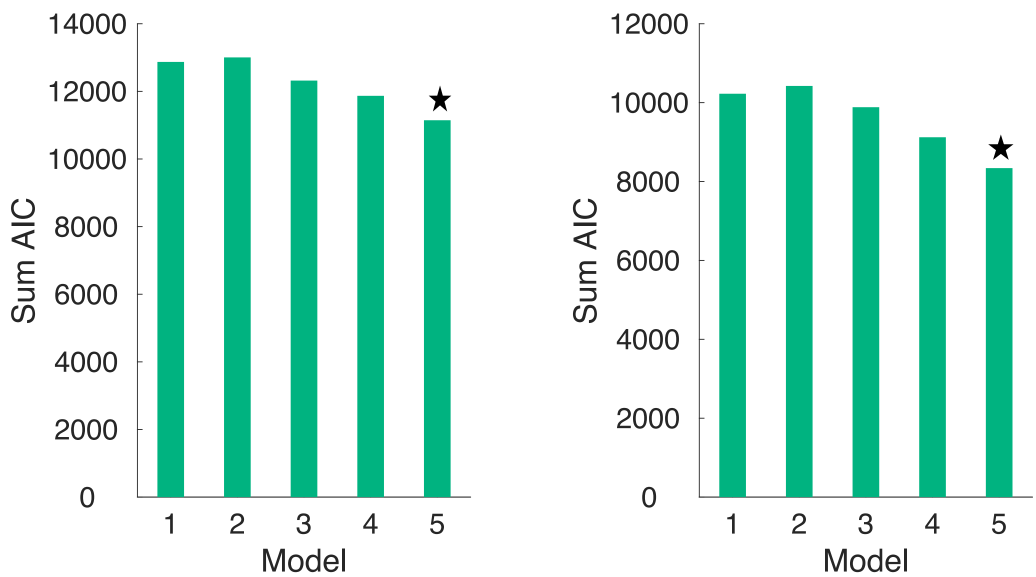

Figure 36. **Modelling perceived fatigue. (a)** List of all models compared. **(b)** Model comparison results for Parkinson's disease patients when they had taken their dopaminergic medication as normal. **(c)** Model comparison results for Parkinson's disease patients when they had withheld their dopaminergic medication since the night before. The x-axis is depicting the model number and the y-axis the sum of the Akaike Information Criterion (AIC) score, indicating that both with and without dopaminergic medication patients' development of perceived fatigue was best described by the Full model (Model 5), as indicated by the star. Additional model comparisons using a Bayesian Information Criterion (BIC) revealed an identical pattern of results. F = Fatigue on trial t; UF = Unrecoverable fatigue; RF = Recoverable fatigue; E = Force exerted; T = time rested.

Next, I directly compared the best fitting parameter values from the winning model for PD ON and OFF. For statistical comparison, a Wilcoxon signed-rank test was used as parameter values were not normally distributed. Two participants were excluded from the analyses who had parameter values greater than three standard deviations above the mean and another two were excluded as they had rated themselves as completely exhausted already in the first third of the task which resulted in poor model fits. As depicted in **Figure 37**, the RF rest parameter (δ), capturing the rate of recovery from fatigue during short periods of rest, was higher for the ON condition compared with the OFF condition. In line with the results from the mixed model, statistical analyses revealed that PD patients ON dopaminergic medication recovered more quickly than PD patients OFF dopaminergic medication, $Z = 1.825$, one-tailed $p = .034$. There was no significant difference in the degree to which effort increased perceived fatigue between the ON and the OFF condition (RF work parameter: $Z = 1.277$, one-tailed $p = .101$; UF parameter: $Z = -0.608$, one-tailed $p = .272$).

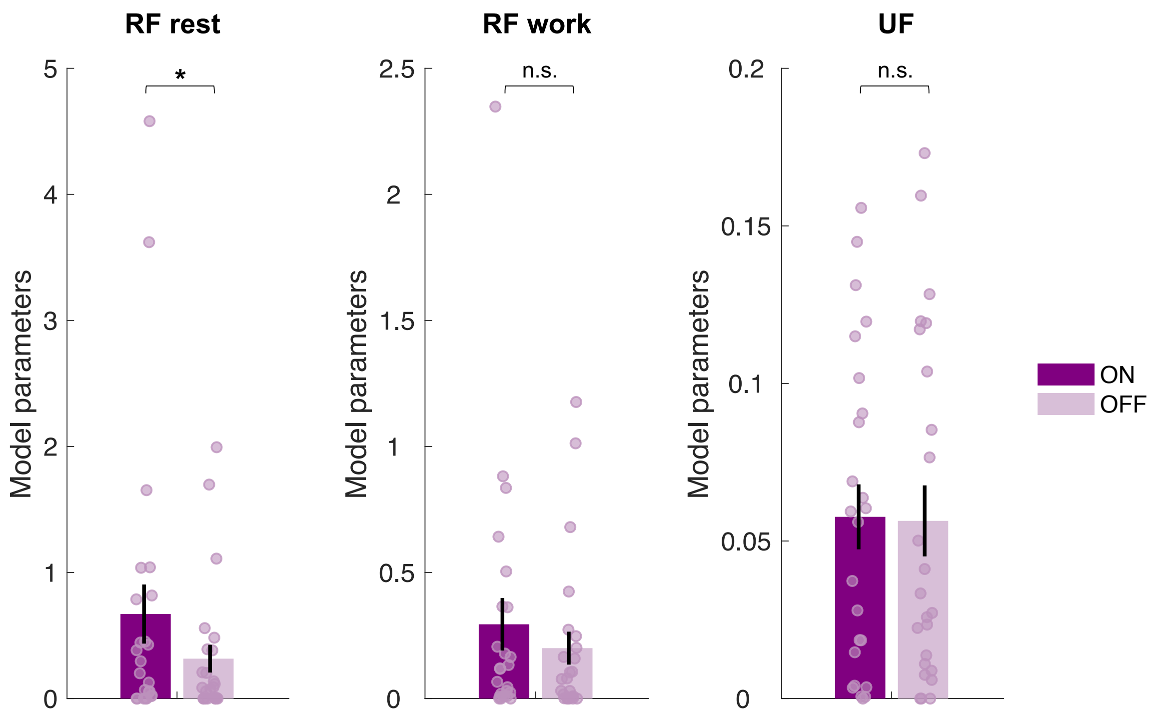

Figure 37. **Model parameters from the Full model.** Mean recoverable fatigue (RF) rest (δ), RF work (α) and unrecoverable fatigue (UF, θ) parameters from the best fitting model separately for Parkinson's disease patients ON and OFF dopaminergic medication, illustrating the beneficial effects of dopaminergic medication on short-term recovery of perceived fatigue during rest. The asterisk indicates a statistically significant difference (p < .05). n.s. = not statistically significant. Each dot represents one subject and error bars reflect SEM.

5.4 Discussion

Patient reports and previous investigations demonstrated that PD patients tend to experience heightened levels of fatigue. Levels of dopamine availability in the brain, which are typically altered in PD, have been suggested to be linked to fatigue, but the precise effects of dopaminergic medications are poorly understood. In this study, I tested the effects of dopaminergic medication in PD patients on the development of self-reported, perceived fatigue by using a within-subjects design in which participants were tested both after they had taken their regular dopaminergic medication (ON) and after they had withheld it since the night before (OFF) and by using a new task in which periods of rest and of varying levels of physical effort as well as rewards were manipulated independently across trials. Statistical analyses and computational modelling showed that dopamine levels in PD patients affected the ability to recover, with patients ON their normal dopaminergic medication showing higher recovery during periods of short rests and thereby lower levels of perceived fatigue. In addition, analyses suggested that dopamine might alter the effects of rewarding action outcomes on the perception of fatigue.

These results overall provide evidence that dopaminergic medication in particular improves the ability to recover and that lowered dopamine levels in unmedicated PD patients may impair their recovery from fatigue after exertion. The fact that patients' level of reported fatigue before the start of the task was similar when being ON and when being OFF dopaminergic medication highlights that the task introduced here allowed for the specific investigation of differential short-term recovery processes between periods of physical work. On the contrary, the effort exerted was not found to play a dominant role in differential fatigue development ON versus OFF medication, suggesting that dopamine may not prevent patients from getting tired through exertion or decrease their sensitivity to efforts. However, the analyses pointed towards slightly more force being produced during the task when in the ON condition, possibly related to an increased motivation to exert effort for rewards when ON dopaminergic medication (Chong et al., 2015; Le Heron et al., 2018b; Soutschek et al., 2020), which may partly explain why fatigue increase in work trials overall was similar between the two conditions.

In either case, the finding of a higher recovery rate following dopaminergic medication and the fact that there was no significant interaction between the effort exerted and the drug state (ON or OFF) might suggest that this improved ability to recover may actually underlie and explain some previously reported links between dopamine levels and effort-based information processing and decision-making in the literature. To gain more insights into the mechanisms and differences, future research could for example more precisely examine the degrees to which PD patients' fatigue recovery and fatigue increase both ON and OFF dopaminergic medication differ from healthy elderly people. To address this question, data collection in an age- and gender-matched control sample had been started but was paused due to the current pandemic. Another open question is where the observed recovery effect stems from. It may indeed be the case that PD patients OFF dopaminergic medication recover less or more slowly from exertion during intermittent periods of rest, or it could be that for them, due to their motor symptoms such as tremor, it is harder to rest properly.

A second finding was the observed interaction effect between dopamine, effort and reward. When tonic dopamine levels were increased in the medicated patients and when comparably high effort was exerted, higher rewards, compared to low rewards, seemed to have a beneficial effect on perceived fatigue, while when lower effort was exerted, lower rewards, compared to higher rewards seemed to have a beneficial effect on fatigue. The former could possibly be due to an increased phasic striatal dopamine response elicited by the higher rewards

(Yoshimi et al., 2011). The latter, however, may partly be explained by the finding that dopaminergic medication as well as higher rewards led to higher force production in the present study. Although in the reported analyses the effect of reward on perceived fatigue could not fully be explained by the effect of force, in combination with the results from **Chapter 4** it overall appears that effects of reward on perceived fatigue following physical exertion are relatively small and likely somewhat dependent on participants' behaviour and generation of force.

A further interesting aspect of the present results is the specific medication that participants had taken or withdrawn. Previous work pointed out that while methylphenidate may reduce subjective fatigue resulting from physical work, levodopa (a precursor of dopamine) and modafinil may rather reduce fatigability during physical work, i.e. the rate at which someone becomes fatigued and at which performance becomes more difficult and typically declines (Lou, 2009). However, the present results suggest that this distinction may not be as straightforward. First, dopaminergic medication in the present study, including levodopa and adjunctive therapy but not methylphenidate, was found to affect fatigue ratings, suggesting that this medication impacts on subjective perceptions of fatigue and not only on associated performance changes. Second, levodopa and adjunctive dopamine therapy primarily increased the rate of decrease in perceived fatigue during short rests rather than reducing the rate of increase in perceived fatigue during physical work, again highlighting that particular attention should be paid to recovery processes and their modulation through certain types of medication.

There are several avenues for future research. For example, in a larger sample, dosage dependency, differential effects of different types of dopaminergic medication which are known to affect different aspects of the dopaminergic system, as well as the interaction with other neurotransmitters that have been linked to the subjective weighting of effort in action selection and performance such as serotonin (Meyniel et al., 2016; see also Pavese et al., 2010) and noradrenaline (Varazzani et al., 2015) could be explored. Also, differential effects of different types of medication on physical versus cognitive fatigability and on perceived fatigue resulting from physical versus cognitive work (see Lou, 2009) could be further examined in order to better understand which processes and systems in the brain play a particular role in the development of and in the recovery from fatigue in PD patients and in other populations.

5.5 Conclusion

Here, it was shown that dopaminergic medication in Parkinson's disease patients impacts on their feeling of fatigue, helping them to recover from physically demanding work during breaks. Results also suggested a potential differential effect of reward on perceived fatigue, dependent on the effort exerted. These results highlight the relevance of particular neurotransmitters, of breaks and recovery processes and perhaps of rewards for the prevention and treatment of abnormal fatigue. In addition, this study demonstrated that the fatigue rating task and the computational fatigue model introduced in this thesis offer an approach to identify and quantify particular parameters for the development of fatigue and may thereby provide a useful tool for the investigation of factors that contribute to and that alleviate different aspects of abnormal fatigue in various patient populations.

6 The relationship between trial-to-trial dynamics of fatigue and motivation

6.1 Introduction

Previous accounts have suggested that feelings of fatigue may affect the willingness to exert effort and thereby behaviour, which may in turn affect feelings of fatigue (Boksem and Tops, 2008; Hockey, 2011; Inzlicht et al., 2014; Kurzban et al., 2013; Müller and Apps, 2019; Pageaux and Lepers, 2016; Tanaka and Watanabe, 2012). However, research on effort-based decision-making has mostly investigated participants' decisions to work or to stop work without specifically considering sensations of fatigue (Chong et al., 2017; Hartmann et al., 2013; Klein-Flügge et al., 2015; Kool et al., 2010; Meyniel et al., 2013). And studies investigating fatigue effects have examined perceived fatigue and its relation to decision-making or to performance either over short or over long timescales but haven't systematically tested trial-by-trial fluctuations (Blain et al., 2019; Meyniel et al., 2014; Wylie et al., 2017).

The work described in the previous chapters of this thesis showed that both the perception of fatigue and the willingness to exert effort fluctuate over repeated exertion and depend on the effort recently exerted and the rest taken, with underlying short-term recoverable and long-term unrecoverable components. It was also shown that fatigue might be associated with an increased focus on the effort costs associated with an action. Yet, how perceived fatigue develops and impacts on people's decisions and vice versa over a series of decisions when people are free to decide when exerting effort for rewards is "worth it" remains to be tested. Therefore, how strongly linked the perception of fatigue and the impact on motivation are, and whether perceived fatigue and motivational fatigue happen on the same timescale, remain open questions.

For this purpose, I developed an effort-based decision-making task similar to the one used for the study described in **Chapter 2** in which participants made a series of choices between a fixed rest/low-reward option and a variable effort/higher-reward option, with two major modifications. First, in the main part of the task participants were now asked on every trial, after they had worked or rested, to rate on a visual analogue scale how tired they felt. Second, effort was operationalised as number of clicks (finger tapping) rather than as the amount of grip force produced in a fixed time window. This allowed me to create an online task which participants could conveniently complete from their preferred location and without special equipment. As such, a second aim of this study was to examine whether this adapted, web-based effort-based decision-making task could reproduce the decision-making patterns seen in the original, lab-based task.

It was hypothesised that fluctuations in perceived fatigue throughout the main part of the task would be predictive of fluctuations in motivation, manifested as an increased rejection of work offers, in particular those high in effort, when fatigue was higher. In turn, the effort exerted was expected to affect and scale changes in perceived fatigue.

6.2 Methods

6.2.1 Participants

Participants were recruited using Prolific (Prolific, UK, available at https://www.prolific.co). They had to be at least 18 years old, be fluent in English and be based in the United Kingdom at the time of participation. A history of good performance in previous studies (having taken part in a minimum of 20 studies on Prolific and having obtained an approval rate of at least 90%) was an additional requirement aimed at ensuring good data quality.

A total of 71 individuals fully completed the study. Of these, one participant was excluded from the analyses because of having re-started the study multiple times and another one was excluded because of a failure to respond within the given time window on more than 10% of trials in the Main task of the experiment. The resulting sample of 69 participants comprised 43 females and had a mean age of 37.36 years (*SD* = 14.47; range 18-74; median = 33). Some of these individuals had previously been diagnosed with a mood and/or anxiety disorder (*n* = 10). Informed consent was given online prior to the start of the task whilst participants remained anonymous. The study was approved by the Central University Research Ethics Committee at the University of Oxford. Participants were paid a base rate of £6 per hour for their time and were given an additional bonus payment depending on their choices and their performance during the task of up to £4.

6.2.2 Materials

To assess fluctuations in motivation and perceived fatigue over repeated exertions, I created an online task combining physical effort-based decisions and fatigue ratings given on a visual analogue scale. In this study effort was operationalised as the number of required clicks with the index finger of one's dominant hand in a fixed time window of 10 seconds. This ensured that different, individualised effort levels could systematically be set without inducing peripheral fatigue and motor slowing (Bächinger et al., 2019).

Stimulus presentation and response collection were implemented using Qualtrics online software (Qualtrics, USA, available at https://www.qualtrics.com) with additional built-in custom JavaScript code. Participants were only allowed to participate if they were using a desktop computer or a laptop to complete the task. Tablets and mobile phones were not permitted to ensure that the induced effort and the appearance of the rating scale were similar across participants. They were free to either use a mouse connected to their desktop computer or laptop or to use the touchpad of their laptop but were instructed not to switch in between. Prior to the main data collection, a few pilot participants were tested to make sure that instructions and comprehension questions were understandable, that participants could easily differentiate between the different effort levels and that they were given enough time to indicate their responses and complete the task. These participants were not included in the analyses.

6.2.3 Experimental design and procedure

Before giving their consent to take part, participants were provided with initial information on the study, the handling of their data, and contact details of the researcher. Only if participants indicated consent and certified that they were 18 years of age or older, they were able to enter the study. On the next screen, participants were reminded of the allowed equipment and the bonus payment that they could earn, and they were asked to complete the different parts of the study without major interruptions as well as to try to avoid distractions.

Similar to the lab-based version described in **Chapter 2**, the experiment consisted of four different parts (**Figure 38**): i) a *Calibration* phase to account for individual differences in skill level, which was completed before the experiment was explained in full to the participants, ii) a *Training* phase in which participants familiarised themselves with the effort levels used in this task, iii) a *Pre-task* aimed at measuring participants' devaluation of rewards (credits) by effort when not fatigued, and iv) the *Main task*, aimed at measuring how participants' devaluation of rewards by effort changes across time depending on participants' fatigue and how, in turn, perceived fatigue fluctuates depending on participants' recent decisions. In both the pre-task and the main task, participants made a series of choices between two alternatives: a rest (baseline) option for a low reward (1 credit), and an effort (work) option for a higher reward.

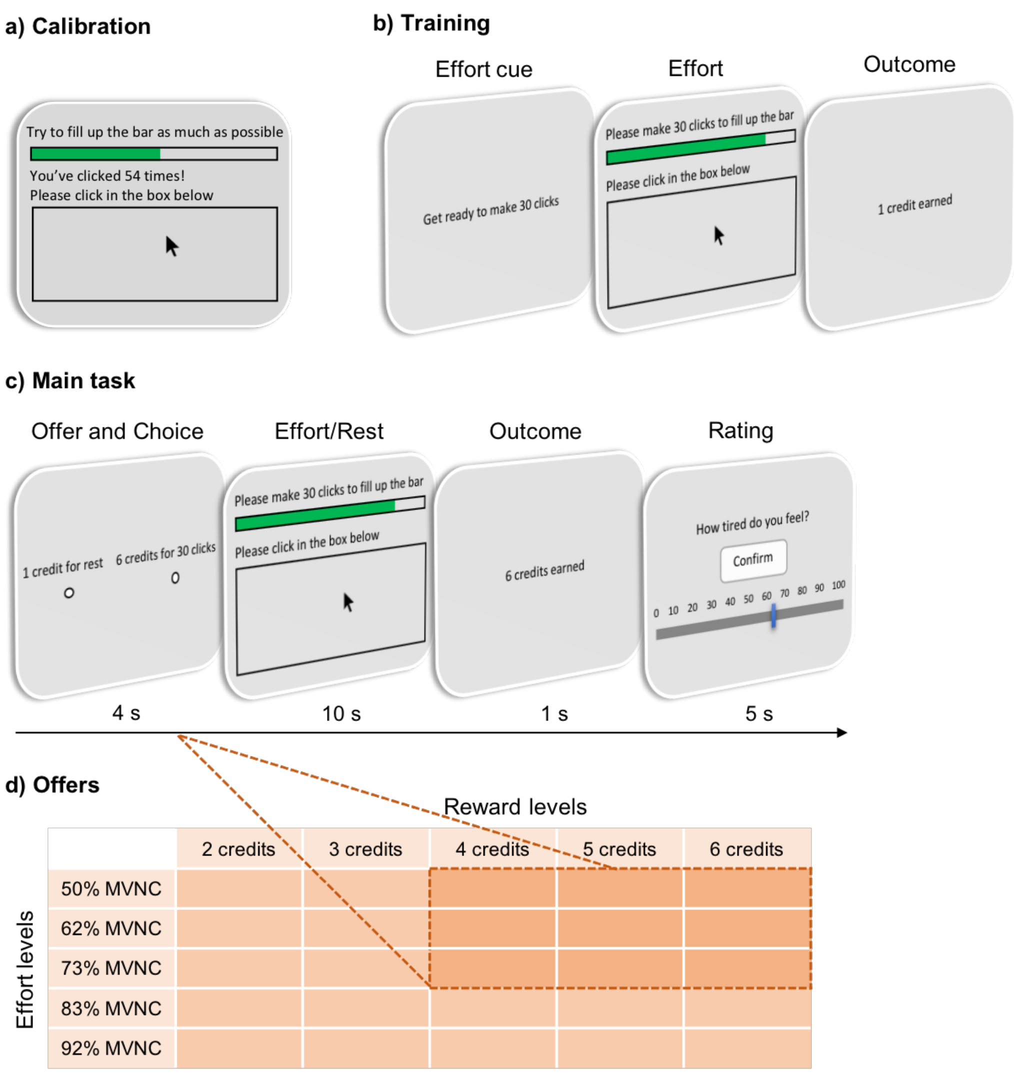

Figure 38. **Trial structure and experimental design. (a)** Each participant's maximum voluntary number of clicks within 10 seconds (MVNC) was measured by asking them to click as many times as they could in a pre-defined box while receiving real-time visual feedback. **(b)** Participants were trained to reach five effort levels which were set depending on their individually calibrated MVNC. **(c)** Trial outline for the Main task. Participants received a variable offer of an effort/reward combination as well as a fixed rest alternative (no effort, 1 credit). If participants accepted the offer, they had to perform the individually required number of clicks in order to receive the offered credits. If they rejected the offer, they rested instead and received one credit. Participants then rated how tired they felt on a visual analogue scale ranging from 0 to 100. Note that while in the main task, 100% of participants' choices lead to actually working or resting, in the Pre-task only 10% of randomly selected trials resulted in the subsequent requirement to work or to rest. In the other cases, the next decision screen was presented. In the pre-task, the rating screen was not included. **(d)** Work offers ranged between 5x5 effort and reward levels in the pre-task and, as highlighted in darker colour, between 3x3 effort and reward levels in the main task.

During *Calibration* (**Figure 38a**), the number of clicks used for the effort levels was calibrated to each participant's capacity. Participants were asked to click as many times as they could in 10 seconds within a predefined box presented on the screen, while a progress bar provided visual feedback on the number of clicks, filling up according to how many times the participant had clicked. In addition, in this calibration phase, the number of clicks was numerically displayed below the progress bar. Participants were told that they would receive higher bonus payments if they clicked more often. This task was repeated three times, with a 5-second rest in between. On each subsequent attempt, participants were encouraged, in text on the top of the screen, to try and beat their score and to do their best. The attempt with the highest number of clicks was used as individual threshold, representing an individual's maximum voluntary number of clicks within 10 seconds (MVNC), for the different levels of effort (50, 62, 73, 83, and 92% MVNC) in the decision task.

Detailed instructions on the overall structure of the pre- and main tasks (**Figures 38c** and **38d**) followed on the next screen. In addition, participants were shown an example of a trial. In these tasks, participants made a series of decisions about their willingness to expend effort to obtain monetary rewards, each involving choosing between two options by clicking on the respective option within 4 seconds: a small reward (1 credit) for 10 seconds of rest, or a higher amount of reward for 10 seconds of work. Work consisted of finger tapping, while the effort levels, i.e. the number of clicks needed to fill up the progress bar, and the rewards on offer were varied independently over trials and presented in a pseudo-random order to ensure that each effort/reward combination was distributed evenly across the task. As such, effects of effort and reward could be tested systematically, and participants were prevented from using any strategy of when to work and when to rest as they did not know what the next trial would be. Each participant was presented with the same sequence to ensure comparability between participants. The number of clicks and the credits associated with them were numerically displayed. Resting was represented by a screen displaying the words “Rest for 10 seconds” and participants were not required to perform any task for 10 seconds. On every trial, it was up to the participants to decide whether they thought the amount of offered credits was worth the required number of clicks. The instructions read that a participant’s total credit score would be used to calculate the bonus payment, and they were encouraged to try and collect as many credits as they could. If participants chose to work but then failed to fill up the progress bar in 10 seconds, they did not receive any credits. Likewise, if participants did not indicate their choice within 4 seconds, they did not receive any credits for this trial and were required to rest for 11 seconds while being reminded to respond faster. On both the decision screen and the work/rest screen, a timer at the bottom left of the screen indicated the time. After work or rest, the number of credits earned on the trial were displayed for 1 second on a subsequent screen. In order to ensure that participants had closely read the instructions and understood the task, two-alternative forced choice comprehension questions about the instructions were included. If participants responded incorrectly to one or more of the comprehension questions (statements), they had two more opportunities to read through the instructions and answer the questions. If any of these questions were answered incorrectly again the study was terminated and the participant was paid £1 for the time spent.

Prior to the pre-task, participants completed a *Training* (**Figure 38b**) to familiarise themselves with the different effort levels. On every trial, participants had to make the respective specified number of clicks to fill up the bar. Clicking was practiced twice for each effort level, resulting in 10 practice trials in total. To make sure that participants carefully and successfully completed this training, they received one credit if they successfully clicked the required number of times, while they received zero credits for a failure.

Before the start of the *Pre-task*, which comprised 75 trials, brief instructions were repeated to remind participants on the task and procedure. Here, work options on every trial consisted of one of five different effort levels that corresponded to 50, 62, 73, 83, and 92% MVNC and one of five different reward levels (2, 3, 4, 5, or 6 credits). Crucially, as this part was aimed at assessing reward discounting by effort in the absence of fatigue, participants did not actually have to make clicks (or rest) on every trial. Instead, only 10% of a participant's decisions resulted in actually working or resting (note that participants were not informed about the percentage). In these cases, participants did not earn credits and a blank screen appeared for 1 second instead of the work or rest screen, followed by the decision screen of the next trial. They were however encouraged to think very carefully about whether they would like to work or not for the number of credits offered and to always be ready to work when they chose to do so.

Following the pre-task, detailed information on how the *Main task*, which consisted of 144 trials, differed from the pre-task was provided. This phase differed in three ways: (i) Only the “higher value” work offers were presented that had been shown to typically be chosen by participants in the pre-task, i.e. combinations of the three highest reward levels (4, 5, and 6 credits) and the three lowest effort levels (50, 62, and 73% MVNC), as choosing to rest when presented with these options would indicate a shift in valuation compared to the pre-task; (ii) every decision resulted in actually working or resting for 10 seconds. That is, if participants chose to rest they got a rest, and if they chose to work they had to make the required number of clicks in order to receive the credits; and (iii) after each work or rest period, participants were asked to rate how tired they felt on a scale ranging from 0 (*not tired at all*) to 100 (*completely exhausted*) by clicking on the scale or dragging the slider and then clicking on a “confirm” button. Participants were asked to give a precise and honest estimation of how tired they felt on each trial, with exhaustion representing the kind of feeling one might experience during a race or some exams (as opposed to sleepiness), and they were assured that their ratings would not affect the options they were presented with. Before the start of the main task, participants completed three practice trials, followed by an initial rating of how tired they felt on the scale. On this initial rating, participants were given as much time as they needed to respond. On each subsequent trial, the starting value on the scale was the value the participant had entered on the previous trial, and participants had a maximum of 5 seconds to either confirm or change this value. A timer at the bottom left of the screen indicated the time remaining.

Finally, demographic information was requested, and participants were given the option to leave a comment.

6.2.4 Statistical analysis

Data were mainly analysed with generalised linear mixed-effects models (GLMMs) using the glmer function and with a linear mixed-effects model (LMM) using the lmer function from the lme4 package (Bates et al., 2015b) in R 3.5.2 (R Core Team, 2018) with the maximum likelihood estimation method. This allowed for the assessment of all trials and variables of interest within a single model, while accounting for potential variability between participants by including a subject-level random intercept. In order to assure a good balance between model interpretability, predictive accuracy and model complexity, the inclusion of interactions and of additional random slopes was determined by model convergence and by model fit as indicated by AIC (Bates et al., 2015a; Burnham and Anderson, 2004; Matuschek et al., 2017). Effects were tested for statistical significance using a Type II Wald chi-square test, i.e. χ^2 and *p*-values refer to comparisons between the tested model and the same model without the respective main effect or interaction of interest.

To investigate how perceived fatigue affects motivation, I analysed choice behaviour with GLMMs, separately for the pre-task and the main task. Choices to work or to rest were coded as binary variables and predicted from the effort and reward levels of the work option on trial *n,* which were coded as continuous variables. Trials with missed choices, which happened very rarely (M = 0.99%, SD = 2.33 in the pre-task; M = 0.99%, SD = 1.65 in the main task) were excluded from the analyses. Crucially, in the main task, the preceding fatigue rating on trial *n*-1 was added as additional predictor.

In addition, to test how closely perceived fatigue, as indicated by participants' ratings, was related to the motivational fatigue that reflects decreases in participants' willingness to work, as derived from fitting the full model introduced in **Chapter 2** to participants' choices, I correlated these model-estimated trial-by-trial fatigue values with trial-by-trial ratings of fatigue for each participant using Pearson correlation coefficients.

To further examine the development of perceived fatigue in the main task, in particular to investigate whether the chosen effort and reward in turn affected changes in perceived fatigue, their effects on changes in participants' fatigue ratings from trial *n*-1 to trial *n,* in trials in which participants had chosen to work, were analysed in an LMM. Dependent variables and predictors were coded as continuous variables. Only trials *n* in which participants had successfully clicked and thus obtained the credits were included in the model, which resulted in the exclusion of $M < 1.39\%$ ($SD < 2.88$) of trials for each level of effort.

6.3 Results

6.3.1 Levels of perceived fatigue affect effort-based decisions

First, I predicted that participants would show a change in their behaviour between the pre-task and the main task of the experiment. This would be consistent with participants becoming more fatigued. As indicated in **Figure 39**, the combination of the three lowest effort levels and the three highest reward levels was almost always selected in the pre-task but less so in the main task. In particular the higher levels of effort for these offers were more likely to be avoided in the first half and even more so in the second half of the main task, indicating that the willingness to exert effort might be affected by fatigue. However, there was considerable variability in choices between participants in the main task, with the majority of participants rejecting several work offers during the task but with nearly half of the sample choosing to rest on less than five trials.

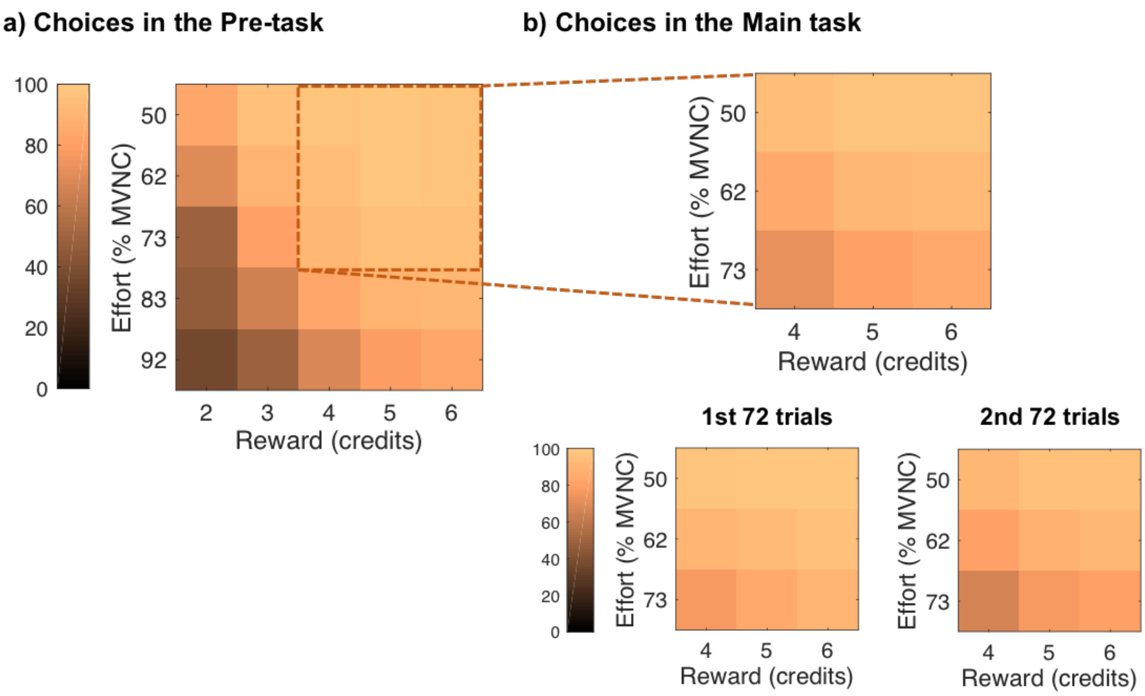

Figure 39. **Choice behaviour in (a) the Pre-task and (b) the Main task, both in total and separately for the first half and the second half.** Illustrated is the mean proportion of accepted work offers as a function of offered reward and effort for each part, indicating that participants were less willing to expend effort for rewards when becoming fatigued.

Next, a GLMM on choices to work or to rest in the pre-task was run with effort level and reward level (z-scored) as predictors. Analyses revealed a significant effect of effort level, $\chi^2(1) = 505.44$, $p < .001$, and reward level, $\chi^2(1) = 569.44$, $p < .001$, of the work offer on participants' choices. In the pre-task, participants were more likely to rest when effort levels were high and more likely to work when reward levels were high (**Figure 39a**).

In a separate GLMM on choices to work or to rest in the main task, I tested whether fatigue ratings on trials *n*-1 were predictive of choice behaviour on trials *n*. Therefore, decisions to work or to rest were predicted from the effort level and the reward associated with the work option as well as the preceding fatigue rating, the interaction of the preceding fatigue rating and the required effort level, the interaction of the preceding fatigue rating and the reward on offer as well as the respective three-way interaction. Predictors were z-scored beforehand for each participant. Further to the subject-level random intercept, a random slope for fatigue ratings was additionally included as this improved model fit, indicated by a lower AIC, and accounted for individual differences in the degree to which perceived fatigue affected choices. Effort significantly predicted choice behaviour in the negative direction, i.e. higher effort levels were chosen less frequently, $\chi^2(1) = 587.975$, $p < .001$, and rewards on offer significantly predicted choice behaviour in the positive direction, i.e. higher rewards were chosen more frequently, $\chi^2(1) = 188.197$, $p < .001$. In addition, higher perceived fatigue prior to the current trial was significantly associated with a tendency to reject work offers, $\chi^2(1) = 33.421$, $p < .001$. It also significantly interacted with the effort level on offer, $\chi^2(1) = 6.110$, $p = .013$, but not with the reward level on offer, $\chi^2(1) = 2.118$, $p = .146$. The three-way interaction of perceived fatigue × effort × reward did not reach significance, $\chi^2(1) = 2.699$, $p = .100$. Thus, with higher feelings of fatigue participants were more likely to reject offers, in particular those that would require the expenditure of higher efforts (see also **Figure 39b**), highlighting that sensations of fatigue are associated with reductions in subsequent motivation.

To further assess how closely related fluctuations in sensations of fatigue and fluctuations in effort-based choices were, model-estimated motivational fatigue, which captures how participants' decisions change throughout the task based on a recoverable and an unrecoverable fatigue component, and fatigue ratings were correlated for each participant. The average correlation coefficient was $r = .523$ ($SD = .415$; median = .667; range: -.572 – .972). Although these values should be interpreted with caution as for participants who rarely chose to rest the model-estimated fatigue might have little or no variance such that the correlation for these participants might be less reliable or not determinable, overall this analysis further supports the assumption that fatigue may affect choices while also pointing towards considerable interindividual differences in effort and fatigue tolerance and perhaps in the conscious awareness of fatigue.

6.3.2 Chosen effort predicts changes in perceived fatigue

Further investigating perceived fatigue, **Figure 40** illustrates that fatigue ratings tended to increase throughout the task, with most participants reporting higher fatigue at the end of the task than at the beginning.

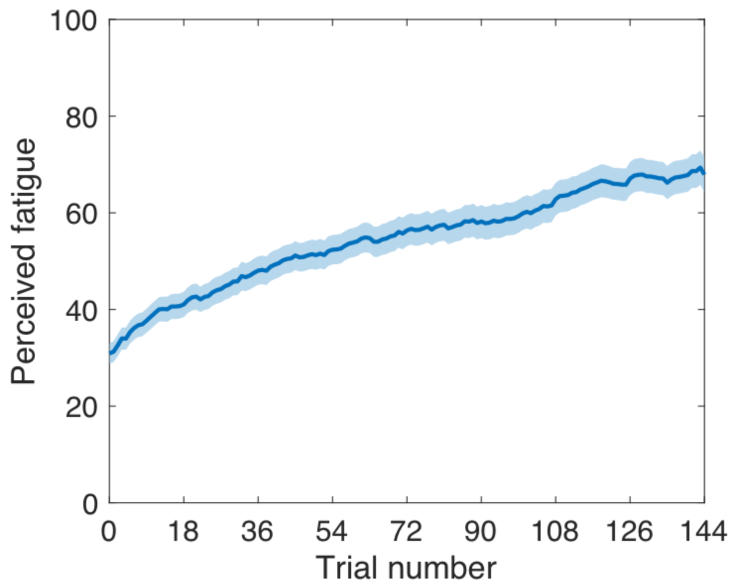

Figure 40. **Perceived fatigue as a function of trial number**. Development of fatigue ratings across the task. Depicted are mean values including standard errors.

Moreover, fatigue ratings fluctuated on a trial-by-trial basis, decreasing when participants had chosen to rest and increasing depending on the amount of effort expended (**Figure 41a**). On the contrary, the amount of reward obtained on a trial was not found to impact changes in perceived fatigue (**Figure 41b**).

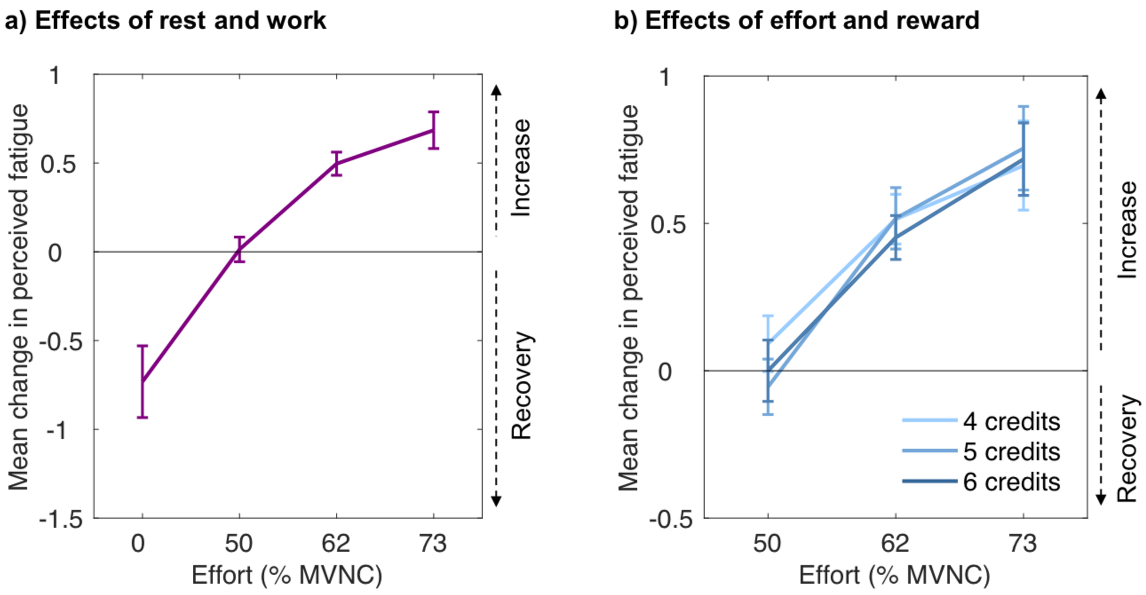

***Figure 41*. Change in perceived fatigue. (a)** Mean change in participants' ratings on the question "How tired do you feel?" from trial *n*-1 to trial *n* as a function of rest (no effort) and work (effort). **(b)** Mean change in participants' ratings on the question "How tired do you feel?" from trial *n*-1 to trial *n* as a function of effort level and reward (credits earned) when participants had chosen to work. Only successful trials in which participants had clicked the required number of times and earned the credits associated with that trial were included. Error bars represent standard errors of the means.

To further test how fatigue ratings fluctuated with the amount of effort chosen and exerted, an LMM was run in which trial-by-trial changes in perceived fatigue were predicted from the chosen effort level and reward and their interaction, including only trials in which participants had accepted the offer and successfully obtained the credits. To improve model fit, indicated by a lower AIC, trial number was added as an additional fixed effect taking into account potential changes over the course of the experiment, similar to the analyses described for Experiment 1 in **Chapter 4**, and in addition a random slope for effort was modelled. Analyses showed that the higher the effort level, the higher the increase in fatigue, $\chi^2(1) = 29.482$, $p < .001$. On the contrary, higher rewarding outcomes were not significantly associated with a higher or with a lower increase in fatigue, $\chi^2(1) = 0.008$, $p = .930$, and also the interaction of effort and reward was not significant, $\chi^2(1) = 0.939$, $p = .333$. Yet, there was a decrease in the change in fatigue over the course of the experiment, $\chi^2(1) = 16.620$, $p < .001$, which might however partly be due to the fact that some participants reached a ceiling, i.e. rated themselves as completely exhausted before the end of the task. These results overall show that perceived fatigue changes moment-to-moment, depending on the effort chosen and successfully exerted, with higher effort resulting in greater increases in fatigue.

6.4 Discussion

In the present study, I investigated the relationship between fluctuations in the feeling of fatigue and fluctuations in motivation over repeated exertions. A physical effort-based decision-making paradigm was employed in an online setting in which participants made a series of choices about their preferences between options that varied in the costs (amount of effort incurred) and in the benefits (monetary rewards) that could be gained. Effort options involved finger tapping with different speed levels in a fixed time window. In addition, participants indicated their fatigue level on a visual analogue scale after each trial.

In line with the hypotheses, perceived fatigue was predictive of subsequent effort-based choices. When levels of perceived fatigue were higher participants were more likely to choose to rest, in particular when higher effort would have been required. In addition, fatigue ratings and model-estimated fatigue based on choices covaried moderately to strongly for the majority of participants. Overall, the present findings lend support to the idea that changes in motivation are related to fluctuations in fatigue and thus to internal states of one's body (Boksem and Tops, 2008; Hockey, 2011; Inzlicht et al., 2014; Kurzban et al., 2013; Meyniel et al., 2014; Müller and Apps, 2019; Tanaka and Watanabe, 2012). The fact that participants' goal was to collect as many credits as possible while not knowing what offers they would be presented with on the following trials supports the notion that changes in motivation were mostly reactive, i.e. affected by fluctuations in fatigue, rather than predictive. Yet, because fatigue levels and the amount of work completed or the rest taken were not manipulated experimentally in this study but depended solely on participants' choices, more work is needed to establish precise causal links between fatigue and motivation and to determine more specifically how closely perceived fatigue and fatigue tolerance are related.

The second finding, namely that perceived fatigue fluctuated with the effort exerted even when people were free to decide whether they found the rewards on offer were worth the effort required, further supports previous accounts highlighting the predominant role of effort expenditure in the development of fatigue, at least in the case of physical work (Müller and Apps, 2019; Pageaux and Lepers, 2016; Tanaka and Watanabe, 2012). In contrast to previous reports in the literature showing that obtaining rewards might reduce perceived fatigue in a working memory task and in a guessing task (Dobryakova et al., 2020, 2018; Hopstaken et al., 2015), in the present study rewards obtained were not found to affect ratings of fatigue. These results overall support the findings from Chapter 4 and suggest that fatigue primarily leads to an increased effort sensitivity rather than to an altered sensitivity to rewards.

Overall, the results demonstrate that the task introduced here is able to produce similar behaviour than the lab-based task introduced in previous chapters. However, it was also found that several participants never or rarely chose to rest in the main task. One explanation for this observation is that the button presses here might not have been perceived as effortful as grip force, or be scaled differently, and have thereby led to lower increases in fatigue and a lower aversion to effort. Possibly, this task could be adapted to induce higher levels of fatigue in a larger part of the sample by modifying the duration of exertion on each trial and in particular by extending the length of the task. Moreover, the observed interindividual variance highlights the need for identifying potential factors and individual characteristics that may contribute to, or modulate, respective interindividual differences.

6.5 Conclusion

These findings highlight the close relation between perceived fatigue and the willingness to exert effort, both significantly depending on the history of effortful exertion and an individual's sensitivity to effort and fluctuating synchronously. Presumably, sensations of fatigue may lead to reductions in motivation, resulting in avoidance of effortful behaviour which may in turn decrease fatigue. Future work could more closely investigate causal links and interindividual differences in this relationship and their potential association with abnormal, persistent fatigue, apathy and various psychological traits and constructs. The online-based task introduced in this chapter, or a modified version of it, provides a means for addressing these questions by allowing for relatively easy and quick data collection in large and heterogenous samples.

7 General Discussion

Performing an action or engaging in an activity typically requires some degree of effort. Constantly we are required to decide whether an expected outcome (reward) is worth the amount of effort required to obtain it. These decisions are highly dynamic and may be depended on context such as for example the potential rewards currently available or the history of effortful exertion and thus fatigue (Boksem and Tops, 2008; Hockey, 2011; Kurzban et al., 2013; Marcora, 2008; Meyniel et al., 2014, 2013; Müller and Apps, 2019). The aim of this thesis was to advance our understanding of the neuroanatomical, neurochemical and computational basis of fatigue – a feeling of exhaustion arising from effortful exertion – and its impact on the willingness to exert effort. I began with outlining existing theoretical and empirical work on fatigue and effort-related motivation and their neural underpinnings. Building on these, I introduced a new theoretical framework and new paradigms assessing fluctuations in effort-based decisions and self-reported fatigue, both in lab-based and web-based settings, alongside a novel computational model that captured underlying hidden components. Using this approach, changes in levels of fatigue over time and their impact on the willingness to exert effort could be precisely measured and quantified. The parameters in this model that quantified a person's sensitivity to effort were shown to be sensitive to intra- and interindividual variability in fatigue and motivation in healthy individuals and to pharmacological manipulation in Parkinson's disease patients.

In the following, I will briefly summarize the main findings from the seven experiments presented in the empirical chapters. I will then outline how the results advance our understanding of state fatigue and motivation as well as of the functions of associated brain regions and will delineate practical implications of this research for work environments and health care while also pointing towards important future research directions.

7.1 Summary of experimental findings

While the willingness to work and exert effort fluctuates and seems to be dependent on previous behaviour and changes in bodily states, studies examining effort-based decisions and their neural basis typically assume that motivation is static. In **Chapter 2** of my thesis, I examined how the value of exerting effort to obtain rewards changes on a moment-to-moment basis, due to fluctuations in internal states putatively linked to fatigue. For this purpose, I developed an effort-based decision-making paradigm in which participants made a series of choices between two alternatives: a rest option for a low reward (1 credit) or a work option, requiring the exertion of one of three levels of effort (grip force) for one of three higher amounts of reward (credits), with effort levels calibrated to each participant's maximum grip strength. Using a new computational model combining previous cost-benefit valuation models with latent fatigue variables in combination with functional Magnetic Resonance Imaging (fMRI), I was able to show how the willingness to exert effort fatigues over trials but also fluctuates trial-to-trial as a function of the recent history of effort and rest during the task. In particular, two hidden fatigue states were identified which led to a decrease in the value of working, resulting in choices to rest, particularly when working would involve higher levels of effort. The value of one state increased after effort but was "recoverable" by rests while the value of a second "unrecoverable" state gradually increased over repeated effortful exertions. The blood oxygen level dependent (BOLD) response in medial and lateral frontal sub-regions of the cortex covaried separately with these two hidden states at the time of making effort-based decisions, with the MFG and the RCZa signalling the unrecoverable component and a distinct RCZp region signalling the recoverable component of fatigue. Activity in a distinct fronto-striatal system comprising the VS and the FP integrated these states to signal the current value of working weighted by levels of fatigue, with variability in people's VS response predictive of the influence fatigue had on effort-based choices. These results highlight that motivation is not static and changes in internal states may lead to an increased sensitivity to efforts, shifting how much value we ascribe to working on a momentary basis.

The results from Chapter 2, together with previous reports, therefore suggest that repeated exertion may lead to a heightened sensitivity to effort which is also reflected in subsequent effort-based decisions. Yet, it remained unclear which particular stages of the decision-making process are susceptible to these fluctuations in effort sensitivity. Prior to decision-making, do people desire to know how effortful something is or how rewarding it is first? **Chapter 3** presented an experiment examining the relationship between information gathering (focus of attention towards effort required versus reward on offer), decision-making and an individual's effort sensitivity. Here, before making cost-benefit decisions similar to the ones described in the main task of Chapter 2, people were required to decide whether they first wanted to see the effort information or whether they first wanted to see the reward information. Results revealed that a preference for effort versus reward information before option selection was associated with an increased effort sensitivity when deciding whether to exert effort for reward, i.e. with an increase likelihood of rejecting work offers that would require the expenditure of high effort. Furthermore, self-report questionnaire measures indicated that those people who report becoming more easily fatigued with exercise, and those who spend less time undergoing demanding exercise in everyday life, and thus who seem to be more sensitive to efforts, typically tend to prioritise effort over reward information in this task. In addition, preferences for effort or reward information also somewhat depended on recent choices to work or rest. These results give a first indication that people's sensitivity to fatigue may shape what information they seek about subsequent behaviours, increasing focus on the effort costs, and may thereby reduce levels of motivation. Importantly, they highlight that not only state fatigue but also trait fatigue may be related to effort-based processes and behaviour.

While the two hidden states affecting effort-based choices over time in the experiment introduced in Chapter 2 were assumed to reflect fatigue and associated heightened sensitivity to efforts, a new study was designed to examine whether direct measures of the perception of effort and fatigue indeed were affected by the same factors and developed in similar ways on a trial-by-trial basis. To this end, three experiments were developed in **Chapter 4**, investigating how perceived effort and perceived fatigue develop over the course of a task as a function of effort exerted, rest taken, and reward obtained. In the first experiment, a physically fatiguing task in which effort levels (amount of grip force) and reward (number of credits awarded for successful exertion) were parametrically varied over trials was employed and trial-by-trial self-report ratings of fatigue were collected. Available credits on every trial were either shown already before exertion (Experiment 1) or only after exertion (Experiment 2) in order to control for potential effects of reward on force production. In a further sample, the same task paradigm was used but trial-by-trial ratings of perceived effort were collected instead (Experiment 3). Results provided evidence for the hypothesis that perceived fatigue increases with effortful exertion and partly decreases with short rest over the course of a task, being susceptible to the same recoverable and unrecoverable components that were found to affect effort-based decisions in Chapter 2. Overall, rewards were not found to particularly affect self-reported fatigue. In addition, the findings revealed that the perception of effort itself increases over repeated exertion. The findings thus suggest a close link between the effects of effortful exertion on perceived fatigue and on the motivation to exert effort and highlight the role of an increased sensitivity to effort costs resulting from repeated exertion.

Using the same task and model as introduced in Chapter 4 (Experiment 1), in **Chapter 5** I tested whether the effects of pharmacological treatment in a population typically affected by abnormal levels of fatigue could be specified with this paradigm and computational approach. In particular, I addressed the question of whether dopaminergic medication in Parkinson’s disease (PD) patients affects the rate of fatigue build-up or the rate of recovery from physically demanding work. Results from 28 PD patients, each tested on two sessions, provided evidence for the hypothesis that PD patients OFF medication show an impaired ability to recover from feelings of fatigue during short periods of rest. Moreover, analyses suggested that dopamine might potentially alter the effects of rewarding action outcomes on the perception of fatigue. In addition to highlighting the relevance of particular neurotransmitters and of recovery processes for feelings of fatigue, this study demonstrated that the fatigue rating task and the computational fatigue model introduced in this thesis may offer a useful approach to identify and quantify specific parameters that underlie fatigue development.

Finally, the study described in **Chapter 6** was designed to provide deeper insights into the relationship between the effects of effortful exertion on the perception of fatigue and the effects of effort expenditure on the motivation to continue to exert effort. To this end, I created an online task in which participants made effort-based decisions, similar to the experiment described in Chapter 2, and additionally indicated their fatigue level on a visual analogue rating scale after each trial. Here, instead of squeezing a hand-held device, work options involved finger tapping with different speed levels. Resembling the findings from Chapters 2 and 4, data from 69 participants showed that both perceived fatigue and effort-based choices depend on an individual's sensitivity to effort and on the history of effortful exertion. Fatigue ratings predicted effort-based choices, and motivational (model-estimated) fatigue and perceived (self-reported) fatigue fluctuated synchronously in many participants, supporting the hypothesised close relationship between perceived fatigue and the willingness to exert effort but also suggesting considerable interindividual differences in the development of fatigue and in particular in its effects on motivation and persistence.

7.2 A neurocognitive framework of fatigue and its impact on motivation

7.2.1 Cognitive and computational mechanisms

The results of these experiments on momentary fluctuations in fatigue and motivation support the concept that exerting effort subsequently leads to a greater cost to performing the same processes such that subsequent acts will become – and feel – more effortful and levels of fatigue increase (Müller and Apps, 2019). As proposed at the beginning of this thesis (see 1.3.2.3), fatigue then reduces the subjective value of exerting effort for rewards by increasing the subjective weight of effort costs. Consequently, people tend to be less willing to engage in the effortful acts that were previously considered "worth it". Here, self-reported fatigue increased and the willingness to exert effort decreased following effortful exertion and both were partially recovered by time resting, while the more effort participants had exerted throughout the task the more tired they felt and the more likely they were to choose to rest. The results further suggested a close relationship between perceptions of effort and perceptions of fatigue, but they also emphasise that the two are not identical. While people did not perceive intermittent rests as effortful, their perceived fatigue decreased during these rest periods but they tended to still feel fatigued to some extent. Furthermore, they suggest that cognitive processes prior to option selection, namely a "bias" towards effort or reward information, are related to variability in effort sensitivity and perhaps to fatigue. Overall, these novel insights support and extend the theoretical framework outlined in Chapter 1 and stress the need for an adaptation of existing effort-discounting models to appropriately capture potential effects of dynamic changes in internal states on value computations.

More specifically, I was also able to identify two fatigue components, one short-term recoverable and one long-term unrecoverable, that described trial-by-trial fluctuations in participants' conscious experience of fatigue and in the degree to which rewards were devalued by effort. These findings bridge over previous lines of research which have either assessed potential changes in fatigue and motivation over short (Meyniel et al., 2014, 2013; Meyniel and Pessiglione, 2014) or over longer timescales (Blain et al., 2019, 2016). The present finding that similar components underly both self-reported fatigue and effort-based choices highlights the close link between the two. Notably, however, the experiments reported in this thesis suggest that people may not only differ in the degree to which effortful exertion increases their levels of fatigue and in particular in their rate of recovery during rests, but they also point towards variability in the degree to which fatigue may affect someone's willingness to continue to exert effort for rewards.

7.2.2 Neural mechanisms

Supporting these computational mechanisms, respective neural correlates were identified in this thesis. Previous research had implicated sensorimotor brain systems in effortful behaviour and suggested that fronto-striatal systems play key roles in ascribing value to rewarding options and in signalling the subjective value of exerting effort to obtain rewards relative to alternative courses of action

(Bonnelle et al., 2016; Botvinick et al., 2009; Burke et al., 2013; Chong et al., 2017; Croxson et al., 2009; Klein-Flügge et al., 2016; Kurniawan et al., 2013; Schmidt et al., 2012; Soutschek et al., 2018). It also suggested a role of dopamine levels in fronto-striatal systems in the motivation to exert effort (Chong et al., 2015; Le Bouc et al., 2016; Soutschek et al., 2020) and potentially in fatigue (Lou, 2009). In addition to their role in option selection, the dACC and DLPFC have also been linked to persisting or switching to different courses of action (Holroyd and McClure, 2015; Holroyd and Yeung, 2012; Kolling et al., 2016a, 2016b; Parvizi et al., 2013; Umemoto et al., 2019) and to monitoring and controlling internal states and the states of other systems (Critchley et al., 2004, 2003; Williamson et al., 2006). In particular the DLPFC was also found to be susceptible to fatigue during decisions involving delay costs (Blain et al., 2019, 2016), and continuous theta-burst stimulation of the DLPFC was very recently linked to effects of fatigue on decisions about whether to exert cognitive effort for monetary rewards (Soutschek and Tobler, 2020). Notably, there is additional evidence that the dACC and DLPFC have similar computational underpinnings (Vassena et al., 2017). They are anatomically and functionally connected with one another as well as with several other systems including parts of the motor system, systems that process interoceptive and exteroceptive information, other regions involved in cognitive processing, and portions of the basal ganglia and of the medial and lateral prefrontal cortex that are linked to option selection and motivation (Haber and Knutson, 2010; Mesulam and Mufson, 1982; Neubert et al., 2015; Pandya et al., 1981; Parent and Parent, 2006; Petrides and Pandya, 2006; Tremblay et al., 2015; Vogt and Pandya, 1987).

The present results extend these findings by suggesting that current levels of fatigue depending on recent exertion and rest, influenced by dopamine levels, modulate activity in dACC and DLPFC and are thereby integrated into the information processed within the VS and FP. Presumably, fatigue arises as a function of effortful exertion within circuits that are recruited during a cognitive or physical task. As levels of fatigue increase with effort, the connections from task-related areas, such as motor or interoceptive areas, to dACC and DLPFC lead to an amplification of the weight given to the costs of exerting effort, which biases evaluations in FP and in particular in the VS. Thereby, fatigue impacts decisions as to whether putting in subsequent efforts to obtain rewarding benefits is worthwhile and decreases motivation (Boksem and Tops, 2008; Hockey, 2011; Kurzban et al., 2013; Müller and Apps, 2019; see also Chapter 1).

Four of the present findings seem particularly relevant for advancing our understanding of the function of these brain systems. First, it was shown that the VS not only processes subjective value but that it also plays a crucial role for people's tendency to persist and that activity in this region may be affected by fatigue. Second, some researchers have argued that the ACC supports the selection and maintenance of options, and thus goal-directed behaviour, in a context-specific manner (Holroyd and Yeung, 2012; Kolling et al., 2016; Kolling et al., 2016) and that more attention should be paid to its sub-regions which may have distinct functional properties (Caruana et al., 2018; Neubert et al., 2015). In line with this assumption, in the present work, in which an extended series of decisions had to be made that involved immediate effort exertion or rest, two sub-regions of the dACC – the RCZp and RCZa – reflected dynamic changes in the subjective discounting of effort costs. During fatiguing tasks, they may thus bias decisions towards resting rather than signalling subjective value per se. Third, very recent work has emphasised that cognition, in particular related to learning, memory and perception, may be subserved by distinct neural processes evolving over multiple timescales (Soltani et al., 2021), and a core role of the dACC for tracking and integrating diverse information over time has been proposed (Procyk et al., 2021). The present results reveal that similar principles of organisation in the brain might also underlie fatigue and recovery and their impact on motivation. And finally, the finding that dopamine deficiency in respective regions was directly related to the rate of recovery from perceived fatigue during short periods of rest further highlights the relevance of dopamine for subjective sensations of fatigue and it stresses the need to differentiate tiring and recovering processes more closely in future research. In fact, abnormal levels of fatigue in certain disorders may not be due to an abnormal experience of exhaustion following exertion but rather to impaired recovery processes, and thus fatigue in these conditions might be qualitatively distinct from state fatigue in otherwise healthy people.

Overall, while the precise brain regions and their respective roles for sensations of fatigue in health and disease and its various effects on motivation and behaviour have yet to be fully identified, the evidence reported here suggests that several areas are likely involved. The potential roles of neurotransmitters other than dopamine which have been implicated in the subjective weighting and allocation of effort during action selection and performance such as serotonin (Meyniel et al., 2016), noradrenaline (Varazzani et al., 2015) and possibly acetylcholine (Sarter et al., 2006), as well as their potential interactive effects, further remain to be established.

7.2.3 Behavioural consequences

While there are of course several factors which can influence motivation and performance, and which may shape them over time, this framework might help explain why previous studies have revealed no simple correlation between activity in certain brain regions, levels of fatigue, and performance measures (Müller and Apps, 2019). For example, when fatigue levels increase and reward levels are not adjusted accordingly, value signals in motivation-related brain regions as well as activity in task-related brain regions might decrease. This will result in the selection of alternative actions, and perhaps of alternative goals, that at this point feel less effortful (or more rewarding), allowing people to recover, or it will lead to impaired performance if the current course of action is continued. Yet, when there is sufficient extrinsic reward or an internal “motivational boost” such that the benefits outweigh the efforts, activity in motivation-associated brain regions might increase such that activation of the respective task-related systems is maintained at a sufficient level, motivation is kept at a sufficient level, people persist and maintain performance and the vigour of actions.

Theoretical accounts in the field of control theory and some recent empirical studies have suggested to conceptualise activity in DLPFC and dACC and associated dopamine levels in these areas in terms of a control signal that typically serves to increase the gain or signal-to-noise ratio in other regions, allowing appropriate information processing in these areas and the overcoming of costs (Kurzban et al., 2013; Manohar et al., 2015; Shenhav et al., 2017, 2013). The present results would suggest that as the costs and thus fatigue increase and motivation decreases, the intensity of this control signal may concomitantly decrease, leading to declines in task accuracy and in the degree to which actions are invigorated.

7.3 Potential limitations and respective future directions

The experimental paradigms and the studies developed and conducted as part of this thesis provide new means for understanding and measuring the dynamics of fatigue and motivation, as outlined in previous and subsequent sections. Several points regarding the comparability between the different experiments and the generalisability of the results more broadly as well as concerning the methodologies chosen shall be briefly discussed in the following alongside respective directions for future research.

Firstly, it has been demonstrated that both fatigue and motivation tend to fluctuate moment-to-moment and gradually increase or decrease, respectively, over repeated exertion. However, it was also shown that individuals differ in the degree to which exertion affects their perceptions of fatigue and the subjective value of work and in how quickly they recover during periods of short rests, as captured by the idiosyncratic recoverable and unrecoverable fatigue parameters. Crucially, the participants in the studies presented in Chapters 2 to 4 were recruited by similar means through the Oxford Psychology Research participant recruitment scheme and respective online bulletin boards and drawn from a similar sample population of university students, university staff and members of the public in the vicinity of Oxford. As such, results of these studies could be directly compared. A somewhat different approach was however chosen for participant recruitment in the online study reported in Chapter 6. Here, participants were recruited through the online platform Prolific, with the sample being more diverse in terms of demographic factors and reported mental health conditions as compared to the samples of healthy young participants that had taken part in the other studies presented in this thesis. Therefore, theoretically, the higher tendency to accept work offers in the online study as compared to the study reported in Chapter 2 could be partly due to differences in sample characteristics (e.g. an individual's general level of motivation) and demographics (e.g. an individual's wealth or income). For example, participants in the online sample might have been more motivated to work because they might have been more incentivised by monetary rewards than the sample in Chapter 2. Yet, a comparison of choice behaviour in the respective pre-tasks as illustrated in Figure 6a and Figure 39a overall does not provide evidence for this assumption. Moreover, whilst baseline fatigue levels were relatively similar between the online study and the fatigue rating task introduced in Chapter 4, the effort levels in the online task, in which effort was operationalised as the speed and number of clicks with one's index finger, lead to smaller increases in fatigue than the effort levels used in Chapter 4 in which effort was operationalised as the amount of grip force to be exerted. For these reasons, differences in task demands seem primarily responsible for observed differences in participant responses between the online study and the other studies. Nevertheless, while the pre-tasks in Chapters 2 and 6 were aimed at quantifying respective interindividual variability in effort-discounting in situations in which fatigue does not accrue, future work including large samples could more specifically assess how such interindividual differences might affect dynamic changes in fatigue and in effort-based choices over the course of repeated exertion as assessed in the main task of the experiments.

A comparison of fatigue ratings and choice behaviour between samples with differing wealth or income could possibly also help dissociate effects of the accumulation of effort from potential effects of the accumulation of rewards, which become correlated especially across the course of the decision-making tasks. Potentially, a modification of these tasks with only a subset of successfully performed trials being rewarded could additionally help somewhat dissociate accumulated efforts from accumulated rewards, although such a design would also increase levels of uncertainty associated with exertion. However, as there is little evidence that people will become sated in such short time frames when accumulating financial rewards in similar tasks, that short breaks would counteract satiety or that satiety would particularly affect effort sensitivity, and participants' goal was to collect as many credits as possible, theoretically it seems unlikely that cumulative reward, and thus satiety, would cause people to decide to take rests regularly in the present experiments. In addition, there was no evidence that fatigue ratings in the ratings tasks generally were strongly impacted by reward magnitude, but instead they largely depended on the effort exerted and could be captured by the same computational model that best predicted dynamics in the willingness to exert effort. Moreover, the underlying UF and RF components fluctuated in brain regions that have previously been linked to effort processing rather than in regions that have been found to particularly signal rewards and their accumulation over time such as the ventromedial prefrontal cortex (Juechems et al., 2017; San-Galli et al., 2018). In sum, although it is possible that accumulated reward also had some influence in particular on choice behaviour, the points outlined above suggest that the computational model presented in this thesis is primarily tracking fatigue induced by effortful exertion and its influence on effort-based choices.

Notably, the pseudorandom trial sequence was similar across participants and experiments in Chapters 4 and 5 and in Chapters 2 (pre-task) and 3, with effort and reward levels varied independently and presented in a pseudorandom order such that each effort/reward combination was distributed relatively evenly across the task. This allowed for the more direct comparison of participants and studies in that observed differences in participant responses and parameter weights could be specifically attributed to individual susceptibility to fatigue between participants and to the variables manipulated between studies. Yet, different trial sequences could be used in future studies to ascertain whether the reported results can indeed be generalised. In contrast, each experiment in this thesis was completed by a different sample in order to prevent potential session effects. The finding that the full fatigue model, including recoverable and unrecoverable components, predicted participants' development of perceived fatigue better than any other tested model in each of the fatigue rating tasks, even though each of these tasks was completed by a different participant sample, does highlight the generalisability of the overall results across participants.

A further aspect regarding the sample chosen and the manipulation used in Chapter 5 of this thesis is worth noting. Here, the role of the neurotransmitter dopamine in the development of fatigue was investigated. In particular, effects of dopaminergic medication on self-reported fatigue over repeated exertion and rests in PD patients was tested. This population was chosen as PD is a neurological disorder in which the majority of patients typically experience heightened levels of fatigue that affect their daily lives even in early stages of the disease (Friedman et al., 2016; Herlofson and Larsen, 2002), and based on previous accounts, dopamine deficiency was hypothesised to be a crucial contributor to abnormal levels of fatigue (Chaudhuri and Behan, 2004, 2000; Friedman et al., 2007). After all, a precise identification and quantification of perceptions of fatigue and respective effects of medication is crucial for detecting and treating abnormalities effectively. However, given that some patients in the present sample were given concomitant dopamine agonists or were on other adjunctive therapies in addition to their levodopa therapy, the specific role of the different components and aspects of the dopaminergic system, such as for example precise brain areas, precise receptor types or dose-dependency, warrants further investigation. This could for example be realised by specifically administering various types of dopaminergic drugs to patient samples as well as to healthy samples who do not suffer from related symptoms such as impairments of the motor system more widely and who have normal baseline dopamine levels, potentially in combination with a placebo condition and with neuroimaging or neurostimulation techniques (Husain and Mehta, 2011; Robbins and Arnsten, 2009). In addition, a comparison to an age- and gender-matched healthy elderly control sample would allow for the better identification of factors such as effort, reward and rest that might be relevant for the abnormal perception of fatigue in PD irrespective of dopamine deficiency. Data collection for such a control sample had been underway but had to be paused due to the COVID-19 pandemic.

Lastly, a general common point of criticism is that participants' behaviour and responses in psychological or economic experiments might be affected by perceived demand characteristics of the experimental situation and thus be susceptible to so-called demand effects, i.e. participants might behave and respond according to what they think is expected of them in the experiment rather than according to how they actually personally think or feel (Nichols and Maner, 2008; Orne, 1962; Zizzo, 2010). Several measures were taken in the studies to minimise such potential effects. First, the purpose and hypotheses of the experiments were not known to participants, the standardised self-report questionnaire assessing general levels of fatigue used in Chapters 3 and 5 was only presented to them after full completion of the experiment, and a new sample was tested in each study. Second, in the decision-making tasks, participants were asked to decide whether they personally considered the reward offered was worth the effort required and whether they thus wanted to accept or reject the offer on a given trial. Third, in the ratings tasks, participants were explicitly instructed that they could increase or decrease their fatigue or effort ratings or that they could keep them constant, that they should respond honestly and that their ratings would neither affect the remainder nor the outcome of the experiment in any way. Nevertheless, while in the present thesis the subjective experience of fatigue has been emphasised as the core characteristic of fatigue and self-report ratings have been considered the most direct assessment of it, a combination of self-reports (Chapters 4 to 6), choice behaviour (Chapters 2, 3, and 6), performance indices as well as physiological measures and other implicit methods, which might for example capture and quantify effort biases as indicated by the results in Chapter 3, might ultimately turn out to be the golden standard for the most coherent examination of fatigue, its effects on motivation and behaviour and the respective underlying mechanisms (see also Kluger et al., 2013). Future work will need to clarify which of these methods or which combination thereof is indeed most promising and most efficient for the assessment of fatigue in health and disease.

7.4 Beyond physical effort: Relevance for the processing of other costs

The work presented here has shed some light on aspects of fatigue and decision-making, yet different questions remain open and might be useful to purse in future research endeavours. First, the focus of the present thesis was to investigate the effects of physical effort and rest on changes in fatigue and motivation and underlying processes in the brain. Previous accounts (Müller and Apps, 2019; Westbrook and Braver, 2015) and the empirical evidence outlined in Chapter 1 suggest that similar mechanisms and partly overlapping brain systems are at play during tasks that are primarily cognitively demanding. However, there may be certain crucial differences as well. For instance, in physical tasks at a certain intensity and certain duration, peripheral signals from the body and activity patterns in motor systems in the brain likely have a considerable impact on sensations of fatigue and associated drops in motivation and performance (Carroll et al., 2017; Kuppuswamy, 2017; Nybo and Secher, 2004; Tanaka and Watanabe, 2012), whereas in cognitive tasks, drops in motivation and performance may have a comparatively higher impact on fatigue (Boksem and Tops, 2008; Dobryakova et al., 2013; Hockey, 2011; Kurzban, 2016; Kurzban et al., 2013; Wylie et al., 2017). Future work should aim to carefully compare different types, patterns and levels of exertion and to systematically test causalities for example by intermixing forced work trials with trials of free choice, by additionally testing samples with different levels of pre-task fatigue or by manipulating rewards and performance feedback. It might also be interesting to further investigate potential interactions between cognitive fatigue and physical fatigue, as many activities in everyday life are not exclusively cognitively or physically demanding.

Second, there are other types of costs such as time (delay) until reward receipt, uncertainty of the action outcome, or the potential availability of alternative rewards (opportunity cost) that are known to affect decision-making and motivation (Frost and McNaughton, 2017; Klein-Flügge et al., 2015; Otto and Daw, 2019; Prévost et al., 2010; Winstanley and Floresco, 2016). The present experiments focused on fluctuations in fatigue and motivation when rewards could be accrued in cases in which each action was associated with a rewarding outcome if performed appropriately. It would be interesting to test how fatigue and motivation vary in cases in which rewards are only obtained after multiple actions, and to further investigate how fatigue interacts with other potential costs. Furthermore, related but possibly somewhat different effects and mechanisms might be observed when people are not exerting effort in order to obtain rewards but in order to avoid negative outcomes or losses instead (e.g. Massar et al., 2020). The paradigms developed here could possibly be adapted and expanded to address these questions and predict choices and performance in these kinds of situations.

7.5 Practical implications

In addition to the theoretical contributions to the understanding of fatigue and motivation, in particular their cognitive, computational and neural underpinnings, the findings of this thesis may also be relevant for people's experience of fatigue and their motivation to engage in demanding activities and ability to regulate them appropriately in everyday life and may thereby help improve their well-being in both professional and casual environments as well as in clinical settings.

7.5.1 Towards more precise assessments

The tasks and the computational model introduced here may open up new possibilities for the measurement and diagnosis of fatigue and motivation. For example, they may help to specifically assess the development of perceived fatigue and resulting fluctuations in motivation in pathological forms of fatigue and impaired motivation that are highly prevalent across a broad range of neurological and psychiatric conditions (Chaudhuri and Behan, 2004; Cullen et al., 2002; Pessiglione et al., 2018). To date, self-report questionnaires are typically used to assess abnormal fatigue and motivation. However, they rarely link the two concepts and rarely take subjective perceptions of effort or recovery effects of rest specifically into account. Therefore, they may not be sensitive enough to differentiate between closely related disorders and symptoms, or to specify effects of treatment. By using a model that can quantify, idiosyncratically, each individual's sensitivity to the efforts they have exerted, and to their recovery through rest, variables underlying fatigue and its impact on motivation can be probed more precisely. Such an approach may help improve differential diagnosis and could shed new light on particular effects of medication. For example, it may prove useful for further characterisation of behavioural patterns which are due to fatigue as compared to apathy and impulsivity in patient populations as well as in otherwise healthy people. Both fatigue and apathy have been associated with disruptions to the willingness to start and to continue to exert effort for reward (Ang et al., 2017; Chaudhuri and Behan, 2004; Husain and Roiser, 2018; Le Heron et al., 2018a; Pessiglione et al., 2018), whereby subjective perceptions of effort and fatigue, and in particular their fluctuations, may be a crucial differentiating factor not to be neglected. It may further help to more closely differentiate fatigue from other related concepts like *anergia* (a loss of energy) or *burnout*.

7.5.2 Towards novel approaches for prevention and treatment

Furthermore, although this thesis did not specifically focus on chronic and pathological fatigue and inactivity, the findings may have implications for appropriate prevention and treatment of these persistent forms. Importantly, they highlight the relevance of rests for recovery from feelings of fatigue and associated decreases in motivation. They also point to dopaminergic medication being effective in the treatment of perceived fatigue resulting from physical activity in disorders with underlying dopaminergic dysfunction, whilst more work is required to determine differential effects of different types of dopaminergic medication. The potential impact of monetary and other types of rewards on the treatment of abnormal forms of fatigue, possibly in combination with specific medication, pose further interesting questions for future research. In addition, it was shown here that an increased focus on effort information is related to an avoidance of highly effortful behaviours and to perceptions of fatigue in everyday life. This may have implications for the development of new treatments. In recent research on depression, a disorder oftentimes associated with heightened levels of fatigue (Demyttenaere et al., 2005; Skapinakis et al., 2004), Attentional bias modification was found to have positive effects on residual symptoms by leading to more adaptive emotion perception and emotion regulation through the reduction of negative attentional biases (Browning et al., 2012; Hilland et al., 2020; Jonassen et al., 2019). Potentially, some similar type of training may prove useful for modifying effort (or reward) biases. This may in turn potentially have direct positive effects on feelings of fatigue, or it may help modify maladaptive forms of behaviour. The latter option is perhaps more likely and may indeed be efficacious as previous work suggested that physical exercise, when done in appropriate form, intensity, duration and intervals, can help improve or prevent fatigue in the long run, potentially also in pathological conditions (Chaudhuri and Behan, 2004; Loy et al., 2013), although it should be noted that the effect of exercise on fatigue in PD is less clear as yet (Elbers et al., 2015; Friedman et al., 2016, 2007).

Notably, in the tasks introduced in the present thesis, effort (and reward) was systematically manipulated and varied to examine its differential role in fatigue and decision-making, and potential detrimental effects of effort expenditure on performance have been highlighted. Notwithstanding, it should be noted that the right amount and intensity of effort expenditure in the right context may also be beneficial in the longer term, as evidenced by improved performance due to training and learning processes (e.g. Friedman et al., 2007; Thorndike, 1912). Other lines of research even suggested that aerobic exercise might in some circumstances have the potential to improve concurrent cognitive performance (Dodwell et al., 2019). Moreover, recent frameworks noted that effort may not only be aversive and perceived as costly but may in some circumstances also be perceived as valuable itself (Inzlicht et al., 2018). The variety of studies and findings highlights again the complexity of the topic in particular and of the human nature in general, reminding us to be careful and thoughtful when interpretating research findings and when formulating guidelines for training and intervention.

7.6 Conclusion

Using a multidisciplinary research approach, this thesis provided new insights into the brain mechanisms underlying fatigue and the dynamics of motivation as reflected in effort-based choices. The findings demonstrate a close relation between an individual's perception of fatigue and his or her willingness to exert effort, both affected by the history of effortful exertion and rests during a task. They also show how fronto-striatal regions, previously implicated in the valuation of effort, may perform distinct computations that underlie how subjective value changes depending on moment-to-moment changes in internal states, and they highlight neural processes that may play a particular role in the recovery during rest.

The theoretical framework of momentary fatigue and motivation to exert effort that was developed might be informative for both psychologists, neuroscientists and economists interested in the basic science of fatigue and decision-making and may perhaps stimulate future research endeavours in these fields. Moreover, the experimental paradigms and the computational model introduced here provide new ways of assessing and quantifying fatigue and motivation in clinical settings and in diverse populations and might thereby help guide future prevention and treatment of abnormal forms of motivation, fatigue and inactivity.

References

Ackerman, P.L., Kanfer, R., Shapiro, S.W., Newton, S., Beier, M.E., 2010. Cognitive fatigue during testing: An examination of trait, time-on-task, and strategy influences. Human Performance 23, 381–402. https://doi.org/10.1080/08959285.2010.517720

Adams, R.A., Huys, Q.J.M., Roiser, J.P., 2016. Computational Psychiatry: Towards a mathematically informed understanding of mental illness. Journal of Neurology, Neurosurgery and Psychiatry 87, 53–63. https://doi.org/10.1136/jnnp-2015-310737

Ainley, V., Apps, M.A.J., Fotopoulou, A., Tsakiris, M., 2016. "Bodily precision": A predictive coding account of individual differences in interoceptive accuracy. Philosophical Transactions of the Royal Society B: Biological Sciences 371, 20160003. https://doi.org/10.1098/rstb.2016.0003

Akaike, H., 1974. A New Look at the Statistical Model Identification. IEEE Transactions on Automatic Control 19, 716–723. https://doi.org/10.1109/TAC.1974.1100705

Alberico, S.L., Cassell, M.D., Narayanan, N.S., 2015. The vulnerable ventral tegmental area in Parkinson's disease. Basal Ganglia 5, 51–55. https://doi.org/10.1016/j.baga.2015.06.001

Amiez, C., Neveu, R., Warrot, D., Petrides, M., Knoblauch, K., Procyk, E., 2013. The location of feedback-related activity in the midcingulate cortex is predicted by local morphology. Journal of Neuroscience 33, 2217–2228. https://doi.org/10.1523/JNEUROSCI.2779-12.2013

Anderson, A.J., Ren, P., Baran, T.M., Zhang, Z., Lin, F., 2019. Insula and putamen centered functional connectivity networks reflect healthy agers' subjective experience of cognitive fatigue in multiple tasks. Cortex 119, 428–440. https://doi.org/10.1016/j.cortex.2019.07.019

Andersson, J.L.R., Hutton, C., Ashburner, J., Turner, R., Friston, K., 2001. Modeling Geometric Deformations in EPI Time Series. NeuroImage 13, 903–919. https://doi.org/10.1006/nimg.2001.0746

Ang, Y.S., Lockwood, P., Apps, M.A.J., Muhammed, K., Husain, M., 2017. Distinct subtypes of apathy revealed by the apathy motivation index. PLoS ONE 12, e0169938. https://doi.org/10.1371/journal.pone.0169938

Apps, M.A.J., Grima, L.L., Manohar, S., Husain, M., 2015. The role of cognitive effort in subjective reward devaluation and risky decision-making. Scientific reports 5, 16880. https://doi.org/10.1038/srep16880

Apps, M.A.J., Ramnani, N., 2014. The anterior cingulate gyrus signals the net value of others' rewards. Journal of Neuroscience 34, 6190–6200. https://doi.org/10.1523/JNEUROSCI.2701-13.2014

Armstrong, M.J., Okun, M.S., 2020. Diagnosis and Treatment of Parkinson Disease: A Review. JAMA 323, 548–560. https://doi.org/10.1001/jama.2019.22360

Arulpragasam, A.R., Cooper, J.A., Nuutinen, M.R., Treadway, M.T., 2018. Corticoinsular circuits encode subjective value expectation and violation for effortful goal-directed behavior. Proceedings of the National Academy of Sciences 115, E5233–E5242. https://doi.org/10.1073/pnas.1800444115

Ashburner, J., Friston, K.J., 2005. Unified segmentation. NeuroImage 26, 839–851. https://doi.org/10.1016/j.neuroimage.2005.02.018
Asplund, C.L., Chee, M.W.L., 2013. Time-on-task and sleep deprivation effects are evidenced in overlapping brain areas. NeuroImage 82, 326–35. https://doi.org/10.1016/j.neuroimage.2013.05.119
Avanzino, L., Tacchino, A., Abbruzzese, G., Quartarone, A., Ghilardi, M.F., Bonzano, L., Ruggeri, P., Bove, M., 2011. Recovery of motor performance deterioration induced by a demanding finger motor task does not follow cortical excitability dynamics. Neuroscience 174, 84–90. https://doi.org/10.1016/j.neuroscience.2010.11.008
Bächinger, M., Lehner, R., Thomas, F., Hanimann, S., Balsters, J., Wenderoth, N., 2019. Human motor fatigability as evoked by repetitive movements results from a gradual breakdown of surround inhibition. eLife 8, e46750. https://doi.org/10.7554/eLife.46750
Balleine, B.W., O'Doherty, J.P., 2010. Human and rodent homologies in action control: Corticostriatal determinants of goal-directed and habitual action. Neuropsychopharmacology 35, 48–69. https://doi.org/10.1038/npp.2009.131
Balsters, J.H., Mantini, D., Apps, M.A.J., Eickhoff, S.B., Wenderoth, N., 2016. Connectivity-based parcellation increases network detection sensitivity in resting state fMRI: An investigation into the cingulate cortex in autism. NeuroImage: Clinical 11, 494–507. https://doi.org/10.1016/j.nicl.2016.03.016
Bates, D., Kliegl, R., Vasishth, S., Baayen, H., 2015a. Parsimonious Mixed Models. arXiv preprint arXiv:1506.04967.
Bates, D., Mächler, M., Bolker, B.M., Walker, S.C., 2015b. Fitting linear mixed-effects models using lme4. Journal of Statistical Software 67. https://doi.org/10.18637/jss.v067.i01
Benoit, C.E., Solopchuk, O., Borragán, G., Carbonnelle, A., Van Durme, S., Zénon, A., 2019. Cognitive task avoidance correlates with fatigue-induced performance decrement but not with subjective fatigue. Neuropsychologia 123, 30–40. https://doi.org/10.1016/j.neuropsychologia.2018.06.017
Bigliassi, M., 2015. Corollary discharges and fatigue-related symptoms: the role of attentional focus. Frontiers in Psychology 6, 1002. https://doi.org/10.3389/fpsyg.2015.01002
Bijleveld, E., 2018. The feeling of effort during mental activity. Consciousness and Cognition 63, 218–227. https://doi.org/10.1016/j.concog.2018.05.013
Blain, B., Hollard, G., Pessiglione, M., 2016. Neural mechanisms underlying the impact of daylong cognitive work on economic decisions. Proceedings of the National Academy of Sciences 113, 6967–6972. https://doi.org/10.1073/pnas.1520527113
Blain, B., Schmit, C., Aubry, A., Hausswirth, C., Le Meur, Y., Pessiglione, M., 2019. Neuro-computational Impact of Physical Training Overload on Economic Decision-Making. Current Biology 29, 3289–3297. https://doi.org/10.1016/j.cub.2019.08.054
Blanchfield, A.W., Hardy, J., De Morree, H.M., Staiano, W., Marcora, S.M., 2014. Talking yourself out of exhaustion: The effects of self-talk on endurance performance. Medicine and Science in Sports and Exercise 46, 998–1007. https://doi.org/10.1249/MSS.0000000000000184
Boksem, M.A.S., Meijman, T.F., Lorist, M.M., 2006. Mental fatigue, motivation

and action monitoring. Biological Psychology 72, 123–132. https://doi.org/10.1016/j.biopsycho.2005.08.007
Boksem, M.A.S., Meijman, T.F., Lorist, M.M., 2005. Effects of mental fatigue on attention: An ERP study. Cognitive Brain Research 25, 107–116. https://doi.org/10.1016/j.cogbrainres.2005.04.011
Boksem, M.A.S., Tops, M., 2008. Mental fatigue: Costs and benefits. Brain Research Reviews 59, 125–139. https://doi.org/10.1016/j.brainresrev.2008.07.001
Bonnelle, V., Manohar, S., Behrens, T., Husain, M., 2016. Individual Differences in Premotor Brain Systems Underlie Behavioral Apathy. Cerebral Cortex 26, 807–819. https://doi.org/10.1093/cercor/bhv247
Bonnelle, V., Veromann, K.R., Burnett Heyes, S., Lo Sterzo, E., Manohar, S., Husain, M., 2015. Characterization of reward and effort mechanisms in apathy. Journal of Physiology Paris 109, 16–26. https://doi.org/10.1016/j.jphysparis.2014.04.002
Borghini, G., Astolfi, L., Vecchiato, G., Mattia, D., Babiloni, F., 2014. Measuring neurophysiological signals in aircraft pilots and car drivers for the assessment of mental workload, fatigue and drowsiness. Neuroscience and Biobehavioral Reviews 44, 58–75. https://doi.org/10.1016/j.neubiorev.2012.10.003
Botvinick, M., Braver, T., 2015. Motivation and Cognitive Control: From Behavior to Neural Mechanism. Annual Review of Psychology 66, 83–113. https://doi.org/10.1146/annurev-psych-010814-015044
Botvinick, M.M., Huffstetler, S., McGuire, J.T., 2009. Effort discounting in human nucleus accumbens. Cognitive, Affective, & Behavioral Neuroscience 9, 16–27. https://doi.org/10.3758/CABN.9.1.16
Boutcher, S.H., Trenske, M., 1990. The Effects of Sensory Deprivation and Music on Perceived Exertion and Affect During Exercise. Journal of Sport and Exercise Psychology 12, 167–176. https://doi.org/10.1123/jsep.12.2.167
Brainard, D.H., 1997. The psychophysics toolbox. Spatial Vision 10, 433–436. https://doi.org/10.1163/156856897X00357
Brehm, J.W., Self, E.A., 1989. The intensity of motivation. Annual Review of Psychology 40, 109–131. https://doi.org/10.1146/annurev.ps.40.020189.000545
Browning, M., Holmes, E.A., Charles, M., Cowen, P.J., Harmer, C.J., 2012. Using attentional bias modification as a cognitive vaccine against depression. Biological Psychiatry 72, 572–579. https://doi.org/10.1016/j.biopsych.2012.04.014
Bültmann, U., Kant, I., Kasl, S. V., Beurskens, A.J.H.M., Van Den Brandt, P.A., 2002. Fatigue and psychological distress in the working population: psychometrics, prevalence, and correlates. Journal of Psychosomatic Research 52, 445–452. https://doi.org/10.1016/S0022-3999(01)00228-8
Burke, C.J., Brünger, C., Kahnt, T., Park, S.Q., Tobler, P.N., 2013. Neural integration of risk and effort costs by the frontal pole: Only upon request. Journal of Neuroscience 33, 1706–1713. https://doi.org/10.1523/JNEUROSCI.3662-12.2013
Burnham, K.P., Anderson, D.R., 2004. Multimodel inference: understanding AIC and BIC in model selection. Sociological Methods & Research 33, 261–304.

https://doi.org/10.1177/0049124104268644
Cain, W.S., Stevens, J.C., 1971. Effort in sustained and phasic handgrip contractions. The American journal of psychology 84, 52–65. https://doi.org/10.2307/1421224
Calderwood, C., Ackerman, P.L., 2011. The relative impact of trait and temporal determinants of subjective fatigue. Personality and Individual Differences 50, 441–445. https://doi.org/10.1016/j.paid.2010.10.030
Camara, E., Manohar, S., Husain, M., 2013. Past rewards capture spatial attention and action choices. Experimental Brain Research 230, 291–300. https://doi.org/10.1007/s00221-013-3654-6
Carroll, T.J., Taylor, J.L., Gandevia, S.C., 2017. Recovery of central and peripheral neuromuscular fatigue after exercise. Journal of Applied Physiology 122, 1068–1076. https://doi.org/10.1152/japplphysiol.00775.2016
Caruana, F., Gerbella, M., Avanzini, P., Gozzo, F., Pelliccia, V., Mai, R., Abdollahi, R.O., Cardinale, F., Sartori, I., Lo Russo, G., Rizzolatti, G., 2018. Motor and emotional behaviours elicited by electrical stimulation of the human cingulate cortex. Brain 141, 3035–3051. https://doi.org/10.1093/brain/awy219
Chalder, T., Berelowitz, G., Pawlikowska, T., Watts, L., Wessely, S., Wright, D., Wallace, E.P., 1993. Development of a fatigue scale. Journal of Psychosomatic Research 37, 147–153. https://doi.org/10.1016/0022-3999(93)90081-P
Chaudhuri, A., Behan, P.O., 2004. Fatigue in neurological disorders. The Lancet 363, 978–988. https://doi.org/10.1016/S0140-6736(04)15794-2
Chaudhuri, A., Behan, P.O., 2000. Fatigue and basal ganglia. Journal of the Neurological Sciences 179, 34–42. https://doi.org/10.1016/S0022-510X(00)00411-1
Chong, T.T.-J., Apps, M., Giehl, K., Sillence, A., Grima, L.L., Husain, M., 2017. Neurocomputational mechanisms underlying subjective valuation of effort costs. PLoS Biology 15, e1002598. https://doi.org/10.1371/journal.pbio.1002598
Chong, T.T.-J., Bonnelle, V., Manohar, S., Veromann, K.-R., Muhammed, K., Tofaris, G.K., Hu, M., Husain, M., 2015. Dopamine enhances willingness to exert effort for reward in Parkinson's disease. Cortex 69, 40–6. https://doi.org/10.1016/j.cortex.2015.04.003
Chong, T.T.J., Bonnelle, V., Husain, M., 2016. Quantifying motivation with effort-based decision-making paradigms in health and disease, in: Progress in Brain Research. Elsevier B.V., pp. 71–100. https://doi.org/10.1016/bs.pbr.2016.05.002
Collignon, A., Maes, F., Delaere, D., Vandermeulen, D., Suetens, P., Marchal, G., 1995. Automated multi-modality image registration based on information theory, in: Bizais, Y., Barillot, C., Di Paola, R. (Eds.), Information Processing in Medical Imaging. Kluwer Academic Publishers, Dordrecht, pp. 263–274.
Cools, R., 2015. The cost of dopamine for dynamic cognitive control. Current Opinion in Behavioral Sciences 4, 152–159. https://doi.org/10.1016/j.cobeha.2015.05.007
Corrado, G., Doya, K., 2007. Understanding neural coding through the model-based analysis of decision making. Journal of Neuroscience 27, 8178–8180.

https://doi.org/10.1523/JNEUROSCI.1590-07.2007
Craig, A.D., 2009. How do you feel - now? The anterior insula and human awareness. Nature Reviews Neuroscience 10, 59–70. https://doi.org/10.1038/nrn2555
Craig, A.D., 2003. Interoception: The sense of the physiological condition of the body. Current Opinion in Neurobiology 13, 500–505. https://doi.org/10.1016/S0959-4388(03)00090-4
Craig, C.L., Marshall, A.L., Sjorstrom, M., Bauman, A.E., Booth, M.L., Ainsworth, B.E., Pratt, M., Ekelund, U., Yngve, A., Sallis, J.F., Oja, P., 2003. International Physical Activity Questionnaire: 12-Country Reliability and Validity. Medicine & Science in Sports & Exercise 35, 1381–1395. https://doi.org/10.1249/01.MSS.0000078924.61453.FB
Crewe, H., Tucker, R., Noakes, T.D., 2008. The rate of increase in rating of perceived exertion predicts the duration of exercise to fatigue at a fixed power output in different environmental conditions. European Journal of Applied Physiology 103, 569–577. https://doi.org/10.1007/s00421-008-0741-7
Critchley, H.D., Corfield, D.R., Chandler, M.P., Mathias, C.J., Dolan, R.J., 2000. Cerebral correlates of autonomic cardiovascular arousal: a functional neuroimaging investigation in humans. The Journal of Physiology 523, 259–270. https://doi.org/10.1111/j.1469-7793.2000.t01-1-00259.x
Critchley, H.D., Mathias, C.J., Josephs, O., O'Doherty, J., Zanini, S., Dewar, B.K., Cipolotti, L., Shallice, T., Dolan, R.J., 2003. Human cingulate cortex and autonomic control: Converging neuroimaging and clinical evidence. Brain 126, 2139–2152. https://doi.org/10.1093/brain/awg216
Critchley, H.D., Tang, J., Glaser, D., Butterworth, B., Dolan, R.J., 2005. Anterior cingulate activity during error and autonomic response. NeuroImage 27, 885–895. https://doi.org/10.1016/j.neuroimage.2005.05.047
Critchley, H.D., Wiens, S., Rotshtein, P., Öhman, A., Dolan, R.J., 2004. Neural systems supporting interoceptive awareness. Nature Neuroscience 7, 189–195. https://doi.org/10.1038/nn1176
Croxson, P.L., Walton, M.E., Reilly, J.X.O., Behrens, T.E.J., Rushworth, M.F.S., 2009. Effort-based cost-benefit valuation and the human brain. Journal of Neuroscience 29, 4531–4541. https://doi.org/10.1523/JNEUROSCI.4515-08.2009
Cullen, W., Kearney, Y., Bury, G., 2002. Prevalence of fatigue in general practice. Irish journal of medical science 171, 10–12. https://doi.org/10.1007/BF03168931
Danielmeier, C., Allen, E.A., Jocham, G., Onur, O.A., Eichele, T., Ullsperger, M., 2015. Acetylcholine mediates behavioral and neural post-error control. Current Biology 25, 1461–1468. https://doi.org/10.1016/j.cub.2015.04.022
De Martino, B., Kumaran, D., Seymour, B., Dolan, R.J., 2006. Frames, biases and rational decision-making in the human brain. Science 313, 684–687. https://doi.org/10.1126/science.1128356
de Morree, H.M., Klein, C., Marcora, S.M., 2014. Cortical substrates of the effects of caffeine and time-on-task on perception of effort. Journal of Applied Physiology 117, 1514–1523. https://doi.org/10.1152/japplphysiol.00898.2013
de Morree, H.M., Marcora, S.M., 2013. Effects of isolated locomotor muscle

fatigue on pacing and time trial performance. European Journal of Applied Physiology 113, 2371–2380. https://doi.org/10.1007/s00421-013-2673-0
Deichmann, R., Gottfried, J.A., Hutton, C., Turner, R., 2003. Optimized EPI for fMRI studies of the orbitofrontal cortex. NeuroImage 19, 430–441. https://doi.org/10.1016/S1053-8119(03)00073-9
Demyttenaere, K., De Fruyt, J., Stahl, S.M., 2005. The many faces of fatigue in major depressive disorder. The International Journal of Neuropsychopharmacology 8, 93–105. https://doi.org/10.1017/S1461145704004729
Dixon, M.L., Christoff, K., 2014. The lateral prefrontal cortex and complex value-based learning and decision making. Neuroscience and Biobehavioral Reviews 45, 9–18. https://doi.org/10.1016/j.neubiorev.2014.04.011
Dobryakova, E., DeLuca, J., Genova, H.M., Wylie, G.R., 2013. Neural Correlates of Cognitive Fatigue: Cortico-Striatal Circuitry and Effort–Reward Imbalance. Journal of the International Neuropsychological Society 19, 849–853. https://doi.org/10.1017/S1355617713000684
Dobryakova, E., Genova, H., Schneider, V., Chiaravalloti, N.D., Spirou, A., Wylie, G.R., DeLuca, J., 2020. Reward presentation reduces on-task fatigue in traumatic brain injury. Cortex 126, 16–25. https://doi.org/10.1016/j.cortex.2020.01.003
Dobryakova, E., Hulst, H.E., Spirou, A., Chiaravalloti, N.D., Genova, H.M., Wylie, G.R., DeLuca, J., 2018. Fronto-striatal network activation leads to less fatigue in multiple sclerosis. Multiple Sclerosis Journal 24, 1174–1182. https://doi.org/10.1177/1352458517717087
Dodwell, G., Müller, H.J., Töllner, T., 2019. Electroencephalographic evidence for improved visual working memory performance during standing and exercise. British Journal of Psychology 110, 400–427. https://doi.org/10.1111/bjop.12352
Draper, A., Koch, R.M., Van Der Meer, J.W.M., Apps, M.A.J., Pickkers, P., Husain, M., Van Der Schaaf, M.E., 2018. Effort but not Reward Sensitivity is Altered by Acute Sickness Induced by Experimental Endotoxemia in Humans. Neuropsychopharmacology 43, 1107–1118. https://doi.org/10.1038/npp.2017.231
Elbers, R.G., Verhoef, J., van Wegen, E.E.H., Berendse, H.W., Kwakkel, G., 2015. Interventions for fatigue in Parkinson's disease. Cochrane Database of Systematic Reviews 10, CD010925. https://doi.org/10.1002/14651858.CD010925.pub2
Elliot, A.J., 2006. The hierarchical model of approach-avoidance motivation. Motivation and Emotion 30, 111–116. https://doi.org/10.1007/s11031-006-9028-7
Enoka, R.M., Baudry, S., Rudroff, T., Farina, D., Klass, M., Duchateau, J., 2011. Unraveling the neurophysiology of muscle fatigue. Journal of Electromyography and Kinesiology 21, 208–219. https://doi.org/10.1016/J.JELEKIN.2010.10.006
Fairclough, S.H., Mulder, L.J.M., 2011. Psychophysiological processes of mental effort investment, in: Wright, R.A., Gendolla, G.H.E. (Eds.), How Motivation Affects Cardiovascular Response: Mechanisms and Applications. American Psychological Association, Washington, DC, pp. 61–76.

Filla, I., Bailey, M.R., Schipani, E., Winiger, V., Mezias, C., Balsam, P.D., Simpson, E.H., 2018. Striatal dopamine D2 receptors regulate effort but not value-based decision making and alter the dopaminergic encoding of cost. Neuropsychopharmacology 43, 2180–2189. https://doi.org/10.1038/s41386-018-0159-9
Fisher, G., 2017. An attentional drift diffusion model over binary-attribute choice. Cognition 168, 34–45. https://doi.org/10.1016/j.cognition.2017.06.007
Fleming, S.M., Dolan, R.J., 2012. The neural basis of metacognitive ability. Phil. Trans. R. Soc. B 367, 1338–1349. https://doi.org/10.1098/rstb.2011.0417
Fleming, S.M., Weil, R.S., Nagy, Z., Dolan, R.J., Rees, G., 2010. Relating Introspective Accuracy to Individual Differences in Brain Structure. Science 329, 1541–1543. https://doi.org/10.1126/science.1191883
Franssen, M., Winward, C., Collett, J., Wade, D., Dawes, H., 2014. Interventions for fatigue in Parkinson's disease: A systematic review and meta-analysis. Movement Disorders 29, 1675–1678. https://doi.org/10.1002/mds.26030
Friedman, J.H., Beck, J.C., Chou, K.L., Clark, G., Fagundes, C.P., Goetz, C.G., Herlofson, K., Kluger, B., Krupp, L.B., Lang, A.E., Lou, J.-S., Marsh, L., Newbould, A., Weintraub, D., 2016. Fatigue in Parkinson's disease: report from a mutidisciplinary symposium. npj Parkinson's Disease 2, 15025. https://doi.org/10.1038/npjparkd.2015.25
Friedman, J.H., Brown, R.G., Comella, C., Garber, C.E., Krupp, L.B., Lou, J.-S., Marsh, L., Nail, L., Shulman, L., Taylor, C.B., 2007. Fatigue in Parkinson's disease: A review. Movement Disorders 22, 297–308. https://doi.org/10.1002/mds.21240
Friston, K.J., Williams, S., Howard, R., Frackowiak, R.S.J., Turner, R., 1996. Movement-Related effects in fMRI time-series. Magnetic Resonance in Medicine 35, 346–355. https://doi.org/10.1002/mrm.1910350312
Frost, R., McNaughton, N., 2017. The neural basis of delay discounting: A review and preliminary model. Neuroscience and Biobehavioral Reviews 79, 48–65. https://doi.org/10.1016/j.neubiorev.2017.04.022
Gendolla, G.H.E., Wright, R.A., Richter, M., 2012. Effort intensity: Some insights from the cardiovascular system, in: Ryan, R.M. (Ed.), The Oxford Handbook of Human Motivation, Oxford Library of Psychology. Oxford University Press, New York, NY, US, pp. 420–438.
Genova, H.M., Rajagopalan, V., DeLuca, J., Das, A., Binder, A., Arjunan, A., Chiaravalloti, N., Wylie, G., 2013. Examination of Cognitive Fatigue in Multiple Sclerosis using Functional Magnetic Resonance Imaging and Diffusion Tensor Imaging. PLoS ONE 8, e78811. https://doi.org/10.1371/journal.pone.0078811
Goetz, C.G., Tilley, B.C., Shaftman, S.R., Stebbins, G.T., Fahn, S., Martinez-Martin, P., Poewe, W., Sampaio, C., Stern, M.B., Dodel, R., Dubois, B., Holloway, R., Jankovic, J., Kulisevsky, J., Lang, A.E., Lees, A., Leurgans, S., LeWitt, P.A., Nyenhuis, D., Olanow, C.W., Rascol, O., Schrag, A., Teresi, J.A., van Hilten, J.J., LaPelle, N., Agarwal, P., Athar, S., Bordelan, Y., Bronte-Stewart, H.M., Camicioli, R., Chou, K., Cole, W., Dalvi, A., Delgado, H., Diamond, A., Dick, J.P., Duda, J., Elble, R.J., Evans, C., Evidente, V.G., Fernandez, H.H., Fox, S., Friedman, J.H., Fross, R.D., Gallagher, D., Goetz, C.G., Hall, D., Hermanowicz, N., Hinson, V., Horn, S., Hurtig, H., Kang, U.J.,

Kleiner-Fisman, G., Klepitskaya, O., Kompoliti, K., Lai, E.C., Leehey, M.L., Leroi, I., Lyons, K.E., McClain, T., Metzer, S.W., Miyasaki, J., Morgan, J.C., Nance, M., Nemeth, J., Pahwa, R., Parashos, S.A., Schneider, J.S.J.S., Schrag, A., Sethi, K., Shulman, L.M., Siderowf, A., Silverdale, M., Simuni, T., Stacy, M., Stern, M.B., Stewart, R.M., Sullivan, K., Swope, D.M., Wadia, P.M., Walker, R.W., Walker, R., Weiner, W.J., Wiener, J., Wilkinson, J., Wojcieszek, J.M., Wolfrath, S., Wooten, F., Wu, A., Zesiewicz, T.A., Zweig, R.M., 2008. Movement Disorder Society-Sponsored Revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS): Scale presentation and clinimetric testing results. Movement Disorders 23, 2129–2170. https://doi.org/10.1002/mds.22340

Grinband, J., Savitskaya, J., Wager, T.D., Teichert, T., Ferrera, V.P., Hirsch, J., 2011. The dorsal medial frontal cortex is sensitive to time on task, not response conflict or error likelihood. NeuroImage 57, 303–311. https://doi.org/10.1016/j.neuroimage.2010.12.027

Haber, S.N., Knutson, B., 2010. The Reward Circuit: Linking Primate Anatomy and Human Imaging. Neuropsychopharmacology 35, 4–26. https://doi.org/10.1038/npp.2009.129

Hartmann, M.N., Hager, O.M., Tobler, P.N., Kaiser, S., 2013. Parabolic discounting of monetary rewards by physical effort. Behavioural Processes 100, 192–196. https://doi.org/10.1016/j.beproc.2013.09.014

Hauser, T.U., Eldar, E., Dolan, R.J., 2017. Separate mesocortical and mesolimbic pathways encode effort and reward learning signals. Proceedings of the National Academy of Sciences 114, E7395–E7404. https://doi.org/10.1073/pnas.1705643114

Helton, W.S., Russell, P.N., 2015. Rest is best: The role of rest and task interruptions on vigilance. Cognition 134, 165–173. https://doi.org/10.1016/J.COGNITION.2014.10.001

Herlofson, K., Larsen, J.P., 2002. Measuring fatigue in patients with Parkinson's disease - The Fatigue Severity Scale. European Journal of Neurology 9, 595–600. https://doi.org/10.1046/j.1468-1331.2002.00444.x

Hilland, E., Landrø, N.I., Harmer, C.J., Browning, M., Maglanoc, L.A., Jonassen, R., 2020. Attentional bias modification is associated with fMRI response toward negative stimuli in individuals with residual depression: A randomized controlled trial. Journal of Psychiatry and Neuroscience 45, 23–33. https://doi.org/10.1503/jpn.180118

Hockey, G.R.J., 2011. A motivational control theory of cognitive fatigue, in: Ackerman, P.L. (Ed.), Cognitive Fatigue: Multidisciplinary Perspectives on Current Research and Future Applications. American Psychological Association, Washington, DC, pp. 167–187.

Hofmans, L., Papadopetraki, D., van den Bosch, R., Määttä, J.I., Froböse, M.I., Zandbelt, B.B., Westbrook, A., Verkes, R.J., Cools, R., 2020. Methylphenidate boosts choices of mental labor over leisure depending on striatal dopamine synthesis capacity. Neuropsychopharmacology 45, 2170–2179. https://doi.org/10.1038/s41386-020-00834-1

Holroyd, C.B., McClure, S.M., 2015. Hierarchical control over effortful behavior by rodent medial frontal cortex: A computational model. Psychological Review 122, 54–83. https://doi.org/10.1037/a0038339

Holroyd, C.B., Yeung, N., 2012. Motivation of extended behaviors by anterior cingulate cortex. Trends in Cognitive Sciences 16, 122–128. https://doi.org/10.1016/j.tics.2011.12.008
Hopstaken, J.F., van der Linden, D., Bakker, A.B., Kompier, M.A.J., 2015. A multifaceted investigation of the link between mental fatigue and task disengagement. Psychophysiology 52, 305–315. https://doi.org/10.1111/psyp.12339
Hou, L.J., Song, Z., Pan, Z.J., Cheng, J.L., Yu, Y., Wang, J., 2016. Decreased Activation of Subcortical Brain Areas in the Motor Fatigue State: An fMRI Study. Frontiers in Psychology 7, 1154. https://doi.org/10.3389/fpsyg.2016.01154
Hsieh, S., Schubert, S., Hoon, C., Mioshi, E., Hodges, J.R., 2013. Validation of the Addenbrooke's Cognitive Examination III in Frontotemporal Dementia and Alzheimer's Disease. Dementia and Geriatric Cognitive Disorders 36, 242–250. https://doi.org/10.1159/000351671
Hunt, L.T., Rutledge, R.B., Malalasekera, W.M.N., Kennerley, S.W., Dolan, R.J., 2016. Approach-Induced Biases in Human Information Sampling. PLOS Biology 14, e2000638. https://doi.org/10.1371/journal.pbio.2000638
Husain, M., Mehta, M.A., 2011. Cognitive enhancement by drugs in health and disease. Trends in Cognitive Sciences 15, 28–36. https://doi.org/10.1016/j.tics.2010.11.002
Husain, M., Roiser, J.P., 2018. Neuroscience of apathy and anhedonia: a transdiagnostic approach. Nature Reviews Neuroscience 19, 470–484. https://doi.org/10.1038/s41583-018-0029-9
Hutchinson, J.C., Tenenbaum, G., 2007. Attention focus during physical effort: The mediating role of task intensity. Psychology of Sport and Exercise 8, 233–245. https://doi.org/10.1016/J.PSYCHSPORT.2006.03.006
Hutton, C., Bork, A., Josephs, O., Deichmann, R., Ashburner, J., Turner, R., 2002. Image distortion correction in fMRI: A quantitative evaluation. NeuroImage 16, 217–240. https://doi.org/10.1006/nimg.2001.1054
Inzlicht, M., Marcora, S.M., 2016. The Central Governor Model of Exercise Regulation Teaches Us Precious Little about the Nature of Mental Fatigue and Self-Control Failure. Frontiers in Psychology 7, 656. https://doi.org/10.3389/fpsyg.2016.00656
Inzlicht, M., Schmeichel, B.J., 2012. What Is Ego Depletion? Toward a Mechanistic Revision of the Resource Model of Self-Control. Perspectives on Psychological Science 7, 450–463. https://doi.org/10.1177/1745691612454134
Inzlicht, M., Schmeichel, B.J., Macrae, C.N., 2014. Why self-control seems (but may not be) limited. Trends in Cognitive Sciences 18, 127–133. https://doi.org/10.1016/j.tics.2013.12.009
Inzlicht, M., Shenhav, A., Olivola, C.Y., 2018. The Effort Paradox: Effort Is Both Costly and Valued. Trends in Cognitive Sciences 22, 337–349. https://doi.org/10.1016/j.tics.2018.01.007
Iodice, P., Calluso, C., Barca, L., Bertollo, M., Ripari, P., Pezzulo, G., 2017a. Fatigue increases the perception of future effort during decision making. Psychology of Sport and Exercise 33, 150–160. https://doi.org/10.1016/j.psychsport.2017.08.013

Iodice, P., Ferrante, C., Brunetti, L., Cabib, S., Protasi, F., Walton, M.E., Pezzulo, G., 2017b. Fatigue modulates dopamine availability and promotes flexible choice reversals during decision making. Scientific Reports 7, 535. https://doi.org/10.1038/s41598-017-00561-6
Johnston, D.W., Allan, J.L., Powell, D.J.H., Jones, M.C., Farquharson, B., Bell, C., Johnston, M., 2019. Why does work cause fatigue? A real-time investigation of fatigue, and determinants of fatigue in nurses working 12-hour shifts. Annals of Behavioral Medicine 53, 551–562. https://doi.org/10.1093/abm/kay065
Jonassen, R., Harmer, C.J., Hilland, E., Maglanoc, L.A., Kraft, B., Browning, M., Stiles, T.C., Haaland, V.Ø., Berge, T., Landrø, N.I., 2019. Effects of Attentional Bias Modification on residual symptoms in depression: A randomized controlled trial. BMC Psychiatry 19, 141. https://doi.org/10.1186/s12888-019-2105-8
Jones, L.A., Hunter, I.W., 1983. Effect of fatigue on force sensation. Experimental Neurology 81, 640–650. https://doi.org/10.1016/0014-4886(83)90332-1
Juechems, K., Balaguer, J., Ruz, M., Summerfield, C., 2017. Ventromedial Prefrontal Cortex Encodes a Latent Estimate of Cumulative Reward. Neuron 93, 705–714. https://doi.org/10.1016/j.neuron.2016.12.038
Kable, J.W., Glimcher, P.W., 2007. The neural correlates of subjective value during intertemporal choice. Nature Neuroscience 10, 1625–1633. https://doi.org/10.1038/nn2007
Kalia, L. V., Lang, A.E., 2015. Parkinson’s disease. The Lancet 386, 896–912. https://doi.org/10.1016/S0140-6736(14)61393-3
Kennerley, S.W., Dahmubed, A.F., Lara, A.H., Wallis, J.D., 2009. Neurons in the Frontal Lobe Encode the Value of Multiple Decision Variables. Journal of Cognitive Neuroscience 21, 1162–1178. https://doi.org/10.1162/jocn.2009.21100
Kennerley, S.W., Wallis, J.D., 2009. Evaluating choices by single neurons in the frontal lobe: Outcome value encoded across multiple decision variables. European Journal of Neuroscience 29, 2061–2073. https://doi.org/10.1111/j.1460-9568.2009.06743.x
Klein-Flügge, M.C., Kennerley, S.W., Friston, K., Bestmann, S., 2016. Neural Signatures of Value Comparison in Human Cingulate Cortex during Decisions Requiring an Effort-Reward Trade-off. Journal of Neuroscience 36, 10002–10015. https://doi.org/10.1523/JNEUROSCI.0292-16.2016
Klein-Flügge, M.C., Kennerley, S.W., Saraiva, A.C., Penny, W.D., Bestmann, S., 2015. Behavioral Modeling of Human Choices Reveals Dissociable Effects of Physical Effort and Temporal Delay on Reward Devaluation. PLoS Computational Biology 11, e1004116. https://doi.org/10.1371/journal.pcbi.1004116
Kluger, B.M., Krupp, L.B., Enoka, R.M., 2013. Fatigue and fatigability in neurologic illnesses: Proposal for a unified taxonomy. Neurology 80, 409–416. https://doi.org/10.1212/WNL.0b013e31827f07be
Kolling, N., Behrens, T.E.J., Wittmann, M.K., Rushworth, M.F.S., 2016a. Multiple signals in anterior cingulate cortex. Current Opinion in Neurobiology 37, 36–43. https://doi.org/10.1016/j.conb.2015.12.007
Kolling, N., Wittmann, M.K., Behrens, T.E.J., Boorman, E.D., Mars, R.B.,

Rushworth, M.F.S., 2016b. Value, search, persistence and model updating in anterior cingulate cortex. Nature Neuroscience 19, 1280–1285. https://doi.org/10.1038/nn.4382
Kool, W., McGuire, J.T., Rosen, Z.B., Botvinick, M.M., 2010. Decision making and the avoidance of cognitive demand. Journal of Experimental Psychology: General 139, 665–682. https://doi.org/10.1037/a0020198
Krajbich, I., Armel, C., Rangel, A., 2010. Visual fixations and the computation and comparison of value in simple choice. Nature Neuroscience 13, 1292–1298. https://doi.org/10.1038/nn.2635
Kroemer, N.B., Guevara, A., Ciocanea Teodorescu, I., Wuttig, F., Kobiella, A., Smolka, M.N., 2014. Balancing reward and work: Anticipatory brain activation in NAcc and VTA predict effort differentially. NeuroImage 102, 510–519. https://doi.org/https://doi.org/10.1016/j.neuroimage.2014.07.060
Krupp, L.B., Larocca, N.G., Muir Nash, J., Steinberg, A.D., 1989. The fatigue severity scale: Application to patients with multiple sclerosis and systemic lupus erythematosus. Archives of Neurology 46, 1121–1123. https://doi.org/10.1001/archneur.1989.00520460115022
Kuppuswamy, A., 2017. The fatigue conundrum. Brain 140, 2240–2245. https://doi.org/10.1093/brain/awx153
Kurniawan, I.T., Guitart-Masip, M., Dayan, P., Dolan, R.J., 2013. Effort and Valuation in the Brain: The Effects of Anticipation and Execution. Journal of Neuroscience 33, 6160–6169. https://doi.org/10.1523/JNEUROSCI.4777-12.2013
Kurniawan, I.T., Guitart-Masip, M., Dolan, R.J., 2011. Dopamine and effort-based decision making. Frontiers in Neuroscience 5, 81. https://doi.org/10.3389/fnins.2011.00081
Kurzban, R., 2016. The sense of effort. Current Opinion in Psychology 7, 67–70. https://doi.org/10.1016/j.copsyc.2015.08.003
Kurzban, R., Duckworth, A., Kable, J.W., Myers, J., 2013. An opportunity cost model of subjective effort and task performance. Behavioral and Brain Sciences 36, 661–679. https://doi.org/10.1017/S0140525X12003196
Le Bouc, R., Rigoux, L., Schmidt, L., Degos, B., Welter, M.-L., Vidailhet, M., Daunizeau, J., Pessiglione, M., 2016. Computational Dissection of Dopamine Motor and Motivational Functions in Humans. Journal of Neuroscience 36, 6623–33. https://doi.org/10.1523/JNEUROSCI.3078-15.2016
Le Heron, C., Apps, M.A.J., Husain, M., 2018a. The anatomy of apathy: A neurocognitive framework for amotivated behaviour. Neuropsychologia 118, 54–67. https://doi.org/10.1016/j.neuropsychologia.2017.07.003
Le Heron, C., Plant, O., Manohar, S., Ang, Y.-S., Jackson, M., Lennox, G., Hu, M.T., Husain, M., 2018b. Distinct effects of apathy and dopamine on effort-based decision-making in Parkinson's disease. Brain 141, 1455–1469. https://doi.org/10.1093/brain/awy110
Le Pelley, M.E., Pearson, D., Griffiths, O., Beesley, T., 2015. When goals conflict with values: counterproductive attentional and oculomotor capture by reward-related stimuli. Journal of Experimental Psychology: General 144, 158–171. https://doi.org/10.1037/xge0000037
Lerdal, A., Bakken, L.N., Kouwenhoven, S.E., Pedersen, G., Kirkevold, M., Finset, A., Kim, H.S., 2009. Poststroke Fatigue-A Review. Journal of Pain

and Symptom Management 38, 928–949. https://doi.org/10.1016/j.jpainsymman.2009.04.028
Lerdal, A., Gulowsen Celius, E., Krupp, L., Dahl, A.A., 2007. A prospective study of patterns of fatigue in multiple sclerosis. European Journal of Neurology 14, 1338–1343. https://doi.org/10.1111/j.1468-1331.2007.01974.x
Lerdal, A., Wahl, A.K., Rustøen, T., Hanestad, B.R., Moum, T., 2005. Fatigue in the general population: a translation and test of the psychometric properties of the Norwegian version of the fatigue severity scale. Scandinavian journal of public health 33, 123–130. https://doi.org/10.1080/14034940410028406
Lim, J., Wu, W.C., Wang, J., Detre, J.A., Dinges, D.F., Rao, H., 2010. Imaging brain fatigue from sustained mental workload: An ASL perfusion study of the time-on-task effect. NeuroImage 49, 3426–3435. https://doi.org/10.1016/j.neuroimage.2009.11.020
Liu, J.Z., Dai, T.H., Sahgal, V., Brown, R.W., Yue, G.H., 2002. Nonlinear cortical modulation of muscle fatigue: A functional MRI study. Brain Research 957, 320–329. https://doi.org/10.1016/S0006-8993(02)03665-X
Lockwood, P.L., Hamonet, M., Zhang, S.H., Ratnavel, A., Salmony, F.U., Husain, M., Apps, M.A.J., 2017. Prosocial apathy for helping others when effort is required. Nature Human Behaviour 1, 0131. https://doi.org/10.1038/s41562-017-0131
Lohse, K.R., Sherwood, D.E., 2011. Defining the Focus of Attention: Effects of Attention on Perceived Exertion and Fatigue. Frontiers in Psychology 2, 332. https://doi.org/10.3389/fpsyg.2011.00332
Lopez-Persem, A., Domenech, P., Pessiglione, M., 2016. How prior preferences determine decision-making frames and biases in the human brain. eLife 5, e20317. https://doi.org/10.7554/eLife.20317
Lorist, M.M., Boksem, M.A.S., Ridderinkhof, K.R., 2005. Impaired cognitive control and reduced cingulate activity during mental fatigue. Cognitive Brain Research 24, 199–205. https://doi.org/10.1016/j.cogbrainres.2005.01.018
Lou, J.-S., 2009. Physical and mental fatigue in Parkinson’s disease: epidemiology, pathophysiology and treatment. Drugs & aging 26, 195–208. https://doi.org/10.2165/00002512-200926030-00002
Loy, B.D., O’Connor, P.J., Dishman, R.K., 2013. The effect of a single bout of exercise on energy and fatigue states: A systematic review and meta-analysis. Fatigue: Biomedicine, Health and Behavior 1, 223–242. https://doi.org/10.1080/21641846.2013.843266
Mackworth, J.F., 1964. Performance Decrement in Vigilance, Threshold, and High-Speed Perceptual Motor Tasks. Canadian journal of psychology 18, 209–23. https://doi.org/10.1037/h0083302
Magno, E., Foxe, J.J., Molholm, S., Robertson, I.H., Garavan, H., 2006. The Anterior Cingulate and Error Avoidance. Journal of Neuroscience 26, 4769–73. https://doi.org/10.1523/JNEUROSCI.0369-06.2006
Manohar, S.G., Chong, T.T.J., Apps, M.A.J., Batla, A., Stamelou, M., Jarman, P.R., Bhatia, K.P., Husain, M., 2015. Reward Pays the Cost of Noise Reduction in Motor and Cognitive Control. Current Biology 25, 1707–1716. https://doi.org/10.1016/j.cub.2015.05.038
Manohar, S.G., Finzi, R.D., Drew, D., Husain, M., 2017. Distinct Motivational Effects of Contingent and Noncontingent Rewards. Psychological Science

28, 1016–1026. https://doi.org/10.1177/0956797617693326
Manohar, S.G., Husain, M., 2013. Attention as foraging for information and value. Frontiers in Human Neuroscience 7, 711. https://doi.org/10.3389/fnhum.2013.00711
Marcora, S., 2009. Perception of effort during exercise is independent of afferent feedback from skeletal muscles, heart, and lungs. Journal of Applied Physiology 106, 2060–2062. https://doi.org/10.1152/japplphysiol.90378.2008
Marcora, S.M., 2008. Do we really need a central governor to explain brain regulation of exercise performance? European Journal of Applied Physiology 104, 929–931. https://doi.org/10.1007/s00421-008-0818-3
Marcora, S.M., Staiano, W., 2010. The limit to exercise tolerance in humans: Mind over muscle? European Journal of Applied Physiology 109, 763–770. https://doi.org/10.1007/s00421-010-1418-6
Marcora, S.M., Staiano, W., Manning, V., 2009. Mental fatigue impairs physical performance in humans. Journal of Applied Physiology 106, 857–864. https://doi.org/10.1152/japplphysiol.91324.2008
Mars, R.B., Shea, N.J., Kolling, N., Rushworth, M.F.S., 2012. Model-based analyses: Promises, pitfalls, and example applications to the study of cognitive control. The Quarterly Journal of Experimental Psychology 65, 252–267. https://doi.org/10.1080/17470211003668272
Massar, S.A.A., Csathó, Á., van der Linden, D., 2018. Quantifying the Motivational Effects of Cognitive Fatigue Through Effort-Based Decision Making. Frontiers in Psychology 9, 843. https://doi.org/10.3389/fpsyg.2018.00843
Massar, S.A.A., Pu, Z., Chen, C., Chee, M.W.L., 2020. Losses Motivate Cognitive Effort More Than Gains in Effort-Based Decision Making and Performance. Frontiers in Human Neuroscience 14, 287. https://doi.org/10.3389/fnhum.2020.00287
Matuschek, H., Kliegl, R., Vasishth, S., Baayen, H., Bates, D., 2017. Balancing Type I error and power in linear mixed models. Journal of Memory and Language 94, 305–315. https://doi.org/10.1016/j.jml.2017.01.001
McGuigan, S., Zhou, S.H., Brosnan, M.B., Thyagarajan, D., Bellgrove, M.A., Chong, T.T.-J., 2019. Dopamine restores cognitive motivation in Parkinson's disease. Brain 142, 719–732. https://doi.org/10.1093/brain/awy341
McGuire, J.T., Botvinick, M.M., 2010. Prefrontal cortex, cognitive control, and the registration of decision costs. Proceedings of the National Academy of Sciences of the United States of America 107, 7922–7926. https://doi.org/10.1073/pnas.0910662107
McMorris, T., Barwood, M., Corbett, J., 2018. Central fatigue theory and endurance exercise: Toward an interoceptive model. Neuroscience and Biobehavioral Reviews 93, 93–107. https://doi.org/10.1016/j.neubiorev.2018.03.024
Meder, D., Kolling, N., Verhagen, L., Wittmann, M.K., Scholl, J., Madsen, K.H., Hulme, O.J., Behrens, T.E.J., Rushworth, M.F.S., 2017. Simultaneous representation of a spectrum of dynamically changing value estimates during decision making. Nature Communications 8, 1942. https://doi.org/10.1038/s41467-017-02169-w
Mesulam, M.M., Mufson, E.J., 1982. Insula of the old world monkey. III: Efferent

cortical output and comments on function. Journal of Comparative Neurology 212, 38–52. https://doi.org/10.1002/cne.902120104
Meyniel, F., Goodwin, G.M., Deakin, J.W., Klinge, C., MacFadyen, C., Milligan, H., Mullings, E., Pessiglione, M., Gaillard, R., 2016. A specific role for serotonin in overcoming effort cost. eLife 5. https://doi.org/10.7554/eLife.17282
Meyniel, F., Pessiglione, M., 2014. Better Get Back to Work: A Role for Motor Beta Desynchronization in Incentive Motivation. Journal of Neuroscience 34, 1–9. https://doi.org/10.1523/JNEUROSCI.1711-13.2014
Meyniel, F., Safra, L., Pessiglione, M., 2014. How the Brain Decides When to Work and When to Rest: Dissociation of Implicit-Reactive from Explicit-Predictive Computational Processes. PLoS Computational Biology 10, e1003584. https://doi.org/10.1371/journal.pcbi.1003584
Meyniel, F., Sergent, C., Rigoux, L., Daunizeau, J., Pessiglione, M., 2013. Neurocomputational account of how the human brain decides when to have a break. Proceedings of the National Academy of Sciences 110, 2641–2646. https://doi.org/10.1073/pnas.1211925110
Micklewright, D., St Clair Gibson, A., Gladwell, V., Al Salman, A., 2017. Development and Validity of the Rating-of-Fatigue Scale. Sports Medicine 47, 2375–2393. https://doi.org/10.1007/s40279-017-0711-5
Milstein, D.M., Dorris, M.C., 2007. The Influence of Expected Value on Saccadic Preparation. Journal of Neuroscience 27, 4810–4818. https://doi.org/10.1523/JNEUROSCI.0577-07.2007
Möckel, T., Beste, C., Wascher, E., 2015. The Effects of Time on Task in Response Selection - An ERP Study of Mental Fatigue. Scientific Reports 5, 10113. https://doi.org/10.1038/srep10113
Mosso, A., Drummond, W.B., Drummond, M.B., 1904. Fatigue, The Science series. G. P. Putnam's Sons/Swan Sonnenschein & Co. Ltd, New York/London.
Mufson, E.J., Mesulam, M.M., 1982. Insula of the old world monkey. II: Afferent cortical input and comments on the claustrum. Journal of Comparative Neurology 212, 23–37. https://doi.org/10.1002/cne.902120103
Muhammed, K., Manohar, S., Ben Yehuda, M., Chong, T.T.J., Tofaris, G., Lennox, G., Bogdanovic, M., Hu, M., Husain, M., 2016. Reward sensitivity deficits modulated by dopamine are associated with apathy in Parkinson's disease. Brain 139, 2706–2721. https://doi.org/10.1093/brain/aww188
Müller, T., Apps, M.A.J., 2019. Motivational fatigue: A neurocognitive framework for the impact of effortful exertion on subsequent motivation. Neuropsychologia 123, 141–151. https://doi.org/10.1016/j.neuropsychologia.2018.04.030
Muraven, M., Baumeister, R.F., 2000. Self-Regulation and Depletion of Limited Resources: Does Self-Control Resemble a Muscle? Psychological Bulletin 126, 247–259. https://doi.org/10.1037/0033-2909.126.2.247
Naccache, L., Dehaene, S., Cohen, L., Habert, M.-O., Guichart-Gomez, E., Galanaud, D., Willer, J.-C., 2005. Effortless control: executive attention and conscious feeling of mental effort are dissociable. Neuropsychologia 43, 1318–1328. https://doi.org/10.1016/j.neuropsychologia.2004.11.024
Neubert, F.-X., Mars, R.B., Sallet, J., Rushworth, M.F.S., 2015. Connectivity

reveals relationship of brain areas for reward-guided learning and decision making in human and monkey frontal cortex. Proceedings of the National Academy of Sciences of the United States of America 112, E2695–E2704. https://doi.org/10.1073/pnas.1410767112
Nichols, A.L., Maner, J.K., 2008. The good-subject effect: Investigating participant demand characteristics. Journal of General Psychology 135, 151–166. https://doi.org/10.3200/GENP.135.2.151-166
Noakes, T.D., 2012. Fatigue is a brain-derived emotion that regulates the exercise behavior to ensure the protection of whole body homeostasis. Frontiers in Physiology 3, 82. https://doi.org/10.3389/fphys.2012.00082
Nuechterlein, K.H., Parasuraman, R., Jiang, Q., 1983. Visual sustained attention: image degradation produces rapid sensitivity decrement over time. Science 220, 327–9. https://doi.org/10.1126/SCIENCE.6836276
Nybo, L., Secher, N.H., 2004. Cerebral perturbations provoked by prolonged exercise. Progress in Neurobiology 72, 223–261. https://doi.org/10.1016/j.pneurobio.2004.03.005
Orne, M.T., 1962. On the social psychology of the psychological experiment: With particular reference to demand characteristics and their implications. American Psychologist 17, 776–783. https://doi.org/10.1037/h0043424
Otto, A.R., Daw, N.D., 2019. The opportunity cost of time modulates cognitive effort. Neuropsychologia 123, 92–105. https://doi.org/10.1016/j.neuropsychologia.2018.05.006
Otto, T., Zijlstra, F.R.H., Goebel, R., 2014. Neural correlates of mental effort evaluation–involvement of structures related to self-awareness. Social Cognitive and Affective Neuroscience 9, 307–315. https://doi.org/10.1093/scan/nss136
Oudiette, D., Vinckier, F., Bioud, E., Pessiglione, M., 2019. A Pavlovian account for paradoxical effects of motivation on controlling response vigour. Scientific Reports 9, 7607. https://doi.org/10.1038/s41598-019-43936-7
Pageaux, B., 2016. Perception of effort in Exercise Science: Definition, measurement and perspectives. European Journal of Sport Science 16, 885–894. https://doi.org/10.1080/17461391.2016.1188992
Pageaux, B., Lepers, R., 2016. Fatigue Induced by Physical and Mental Exertion Increases Perception of Effort and Impairs Subsequent Endurance Performance. Frontiers in Physiology 7, 587. https://doi.org/10.3389/fphys.2016.00587
Palomero-Gallagher, N., Mohlberg, H., Zilles, K., Vogt, B., 2008. Cytology and receptor architecture of human anterior cingulate cortex. Journal of Comparative Neurology 508, 906–926. https://doi.org/10.1002/cne.21684
Pandya, D.N., Vanhoesen, G.W., Mesulam, M.M., 1981. Efferent connections of the cingulate gyrus in the rhesus monkey. Experimental Brain Research 42, 319–330. https://doi.org/10.1007/BF00237497
Parent, M., Parent, A., 2006. Single-axon tracing study of corticostriatal projections arising from primary motor cortex in primates. The Journal of Comparative Neurology 496, 202–213. https://doi.org/10.1002/cne.20925
Parry, D., Chinnasamy, C., Papadopoulou, E., Noakes, T., Micklewright, D., 2011. Cognition and performance: Anxiety, mood and perceived exertion among Ironman triathletes. British Journal of Sports Medicine 45, 1088–

1094. https://doi.org/10.1136/bjsm.2010.072637
Parvizi, J., Rangarajan, V., Shirer, W.R., Desai, N., Greicius, M.D., 2013. The will to persevere induced by electrical stimulation of the human cingulate gyrus. Neuron 80, 1359–1367. https://doi.org/10.1016/j.neuron.2013.10.057
Pasquereau, B., Turner, R.S., 2013. Limited encoding of effort by dopamine neurons in a cost-benefit trade-off task. Journal of neuroscience 33, 8288–300. https://doi.org/10.1523/JNEUROSCI.4619-12.2013
Pavese, N., Metta, V., Bose, S.K., Chaudhuri, K.R., Brooks, D.J., 2010. Fatigue in Parkinson's disease is linked to striatal and limbic serotonergic dysfunction. Brain 133, 3434–3443. https://doi.org/10.1093/brain/awq268
Pessiglione, M., Vinckier, F., Bouret, S., Daunizeau, J., Le Bouc, R., 2018. Why not try harder? Computational approach to motivation deficits in neuro-psychiatric diseases. Brain 141, 629–650. https://doi.org/10.1093/brain/awx278
Petrides, M., Pandya, D.N., 2006. Efferent association pathways originating in the caudal prefrontal cortex in the macaque monkey. Journal of Comparative Neurology 498, 227–251. https://doi.org/10.1002/cne.21048
Petrides, M., Pandya, D.N., 1999. Dorsolateral prefrontal cortex: comparative cytoarchitectonic analysis in the human and the macaque brain and corticocortical connection patterns. European Journal of Neuroscience 11, 1011–1036. https://doi.org/10.1046/j.1460-9568.1999.00518.x
Pine, A., Seymour, B., Roiser, J.P., Bossaerts, P., Friston, K.J., Curran, H.V., Dolan, R.J., 2009. Encoding of marginal utility across time in the human brain. Journal of Neuroscience 29, 9575–9581. https://doi.org/10.1523/JNEUROSCI.1126-09.2009
Pooresmaeili, A., Wannig, A., Dolan, R.J., 2015. Receipt of reward leads to altered estimation of effort. Proceedings of the National Academy of Sciences of the United States of America 112, 13407–13410. https://doi.org/10.1073/pnas.1507527112
Prévost, C., Pessiglione, M., Metereau, E., Clery-Melin, M.-L., Dreher, J.-C., 2010. Separate Valuation Subsystems for Delay and Effort Decision Costs. Journal of Neuroscience 30, 14080–14090. https://doi.org/10.1523/JNEUROSCI.2752-10.2010
Procyk, E., Fontanier, V., Sarazin, M., Delord, B., Goussi, C., Wilson, C.R.E., 2021. The midcingulate cortex and temporal integration, in: International Review of Neurobiology. Academic Press Inc., pp. 395–419. https://doi.org/10.1016/bs.irn.2020.12.004
Procyk, E., Wilson, C.R.E., Stoll, F.M., Faraut, M.C.M., Petrides, M., Amiez, C., 2016. Midcingulate Motor Map and Feedback Detection: Converging Data from Humans and Monkeys. Cerebral Cortex 26, 467–476. https://doi.org/10.1093/cercor/bhu213
Ricci, J.A., Chee, E., Lorandeau, A.L., Berger, J., 2007. Fatigue in the U.S. Workforce: Prevalence and Implications for Lost Productive Work Time. Journal of Occupational and Environmental Medicine 49, 1–10. https://doi.org/10.1097/01.jom.0000249782.60321.2a
Ridderinkhof, K.R., Ullsperger, M., Crone, E.A., Nieuwenhuis, S., 2004. The role of the medial frontal cortex in cognitive control. Science 306, 443–447. https://doi.org/10.1126/science.1100301

Robbins, T.W., Arnsten, A.F.T., 2009. The Neuropsychopharmacology of Fronto-Executive Function: Monoaminergic Modulation. Annual Review of Neuroscience 32, 267–287. https://doi.org/10.1146/annurev.neuro.051508.135535
Rudebeck, P.H., Walton, M.E., Smyth, A.N., Bannerman, D.M., Rushworth, M.F.S., 2006. Separate neural pathways process different decision costs. Nature Neuroscience 9, 1161–1168. https://doi.org/10.1038/nn1756
Rutledge, R.B., Skandali, N., Dayan, P., Dolan, R.J., 2014. A computational and neural model of momentary subjective well-being. PNAS 111, 12252–12257. https://doi.org/10.1073/pnas.1407535111
Ryan, J.L., Carroll, J.K., Ryan, E.P., Mustian, K.M., Fiscella, K., Morrow, G.R., 2007. Mechanisms of Cancer-Related Fatigue. The Oncologist 12, 22–34. https://doi.org/10.1634/theoncologist.12-s1-22
Salamone, J.D., Correa, M., Farrar, A., Mingote, S.M., 2007. Effort-related functions of nucleus accumbens dopamine and associated forebrain circuits. Psychopharmacology 191, 461–482. https://doi.org/10.1007/s00213-006-0668-9
Salamone, J.D., Yohn, S.E., López-Cruz, L., San Miguel, N., Correa, M., 2016. Activational and effort-related aspects of motivation: Neural mechanisms and implications for psychopathology. Brain 139, 1325–1347. https://doi.org/10.1093/brain/aww050
San-Galli, A., Varazzani, C., Abitbol, R., Pessiglione, M., Bouret, S., 2018. Primate Ventromedial Prefrontal Cortex Neurons Continuously Encode the Willingness to Engage in Reward-Directed Behavior. Cerebral Cortex 28, 73–89. https://doi.org/10.1093/cercor/bhw351
Sarter, M., Gehring, W.J., Kozak, R., 2006. More attention must be paid: The neurobiology of attentional effort. Brain Research Reviews 51, 145–160. https://doi.org/10.1016/j.brainresrev.2005.11.002
Schifitto, G., Friedman, J.H., Oakes, D., Shulman, L., Comella, C.L., Marek, K., Fahn, S., Parkinson Study Group ELLDOPA, 2008. Fatigue in levodopa-naive subjects with Parkinson disease. Neurology 71, 481–5. https://doi.org/10.1212/01.wnl.0000324862.29733.69
Schmidt, L., Lebreton, M., Cléry-Melin, M.L., Daunizeau, J., Pessiglione, M., 2012. Neural mechanisms underlying motivation of mental versus physical effort. PLoS Biology 10, e1001266. https://doi.org/10.1371/journal.pbio.1001266
Schwarz, G., 1978. Estimating the Dimension of a Model. The Annals of Statistics 6, 461–464. https://doi.org/10.1214/aos/1176344136
Sepulveda, P., Usher, M., Davies, N., Benson, A., Ortoleva, P., De Martino, B., 2020. Visual attention modulates the integration of goal-relevant evidence and not value. eLife 9, e60705. https://doi.org/10.7554/eLife.60705
Shadmehr, R., Reppert, T.R., Summerside, E.M., Yoon, T., Ahmed, A.A., 2019. Movement Vigor as a Reflection of Subjective Economic Utility. Trends in Neurosciences 42, 323–336. https://doi.org/10.1016/j.tins.2019.02.003
Shalev, L., Ben-Simon, A., Mevorach, C., Cohen, Y., Tsal, Y., 2011. Conjunctive Continuous Performance Task (CCPT)-A pure measure of sustained attention. Neuropsychologia 49, 2584–2591. https://doi.org/10.1016/j.neuropsychologia.2011.05.006

Sheikh, J.I., Yesavage, J.A., 1986. Geriatric Depression Scale (GDS): recent evidence and development of a shorter version. Clinical gerontologist 5, 165–173. https://doi.org/10.1300/J018v05n01_09

Shenhav, A., Botvinick, M.M., Cohen, J.D., 2013. The expected value of control: An integrative theory of anterior cingulate cortex function. Neuron 79, 217–240. https://doi.org/10.1016/j.neuron.2013.07.007

Shenhav, A., Musslick, S., Lieder, F., Kool, W., Griffiths, T.L., Cohen, J.D., Botvinick, M.M., 2017. Toward a Rational and Mechanistic Account of Mental Effort. Annual Review of Neuroscience 40, 99–124. https://doi.org/10.1146/annurev-neuro-072116-031526

Shigihara, Y., Tanaka, M., Ishii, A., Tajima, S., Kanai, E., Funakura, M., Watanabe, Y., 2013. Two different types of mental fatigue produce different styles of task performance. Neurology Psychiatry and Brain Research 19, 5–11. https://doi.org/10.1016/j.npbr.2012.07.002

Sidhu, S.K., Cresswell, A.G., Carroll, T.J., 2013. Corticospinal Responses to Sustained Locomotor Exercises: Moving Beyond Single-Joint Studies of Central Fatigue. Sports Medicine 43, 437–449. https://doi.org/10.1007/s40279-013-0020-6

Sinha, N., Manohar, S., Husain, M., 2013. Impulsivity and apathy in Parkinson's disease. Journal of Neuropsychology 7, 255–283. https://doi.org/10.1111/jnp.12013

Skapinakis, P., Lewis, G., Mavreas, V., 2004. Temporal Relations Between Unexplained Fatigue and Depression: Longitudinal Data From an International Study in Primary Care. Psychosomatic Medicine 66, 330–335. https://doi.org/10.1097/01.psy.0000124757.10167.b1

Skapinakis, P., Lewis, G., Meltzer, H., 2003. Clarifying the relationship between unexplained chronic fatigue and psychiatric morbidity: Results from a community survey in Great Britain. International Review of Psychiatry 15, 57–64. https://doi.org/10.1080/0954026021000045958

Skorvanek, M., Gdovinova, Z., Rosenberger, J., Ghorbani Saeedian, R., Nagyova, I., Groothoff, J.W., van Dijk, J.P., 2015. The associations between fatigue, apathy, and depression in Parkinson's disease. Acta Neurologica Scandinavica 131, 80–87. https://doi.org/10.1111/ane.12282

Smets, E.M.A., Garssen, B., Bonke, B., De Haes, J.C.J.M., 1995. The multidimensional Fatigue Inventory (MFI) psychometric qualities of an instrument to assess fatigue. Journal of Psychosomatic Research 39, 315–325. https://doi.org/10.1016/0022-3999(94)00125-O

Sockeel, P., Dujardin, K., Devos, D., Denève, C., Destée, A., Defebvre, L., 2006. The Lille apathy rating scale (LARS), a new instrument for detecting and quantifying apathy: Validation in Parkinson's disease. Journal of Neurology, Neurosurgery and Psychiatry 77, 579–584. https://doi.org/10.1136/jnnp.2005.075929

Soltani, A., Murray, J.D., Seo, H., Lee, D., 2021. Timescales of cognition in the brain. Current Opinion in Behavioral Sciences 41, 30–37. https://doi.org/10.1016/j.cobeha.2021.03.003

Soutschek, A., Gvozdanovic, G., Kozak, R., Duvvuri, S., de Martinis, N., Harel, B., Gray, D.L., Fehr, E., Jetter, A., Tobler, P.N., 2020. Dopaminergic D1 Receptor Stimulation Affects Effort and Risk Preferences. Biological

Psychiatry 87, 678–685. https://doi.org/10.1016/j.biopsych.2019.09.002
Soutschek, A., Kang, P., Ruff, C.C., Hare, T.A., Tobler, P.N., 2018. Brain Stimulation Over the Frontopolar Cortex Enhances Motivation to Exert Effort for Reward. Biological Psychiatry 84, 38–45. https://doi.org/10.1016/j.biopsych.2017.11.007
Soutschek, A., Tobler, P.N., 2020. Causal role of lateral prefrontal cortex in mental effort and fatigue. Human Brain Mapping 41, 4630–4640. https://doi.org/10.1002/hbm.25146
St. Clair Gibson, A., Baden, D.A., Lambert, M.I., Lambert, E.V., Harley, Y.X.R., Hampson, D., Russell, V.A., Noakes, T.D., 2003. The conscious perception of the sensation of fatigue. Sports Medicine 33, 167–176. https://doi.org/10.2165/00007256-200333030-00001
Stahl, S.M., 2002. The psychopharmacology of energy and fatigue. The Journal of clinical psychiatry 63, 7–8. https://doi.org/10.4088/jcp.v63n0102
Staiano, W., Bosio, A., de Morree, H.M., Rampinini, E., Marcora, S., 2018. The cardinal exercise stopper: Muscle fatigue, muscle pain or perception of effort?, in: Progress in Brain Research. Elsevier, pp. 175–200. https://doi.org/10.1016/bs.pbr.2018.09.012
Stephan, K.E., Manjaly, Z.M., Mathys, C.D., Weber, L.A.E., Paliwal, S., Gard, T., Tittgemeyer, M., Fleming, S.M., Haker, H., Seth, A.K., Petzschner, F.H., 2016. Allostatic Self-efficacy: A Metacognitive Theory of Dyshomeostasis-Induced Fatigue and Depression. Frontiers in Human Neuroscience 10, 550. https://doi.org/10.3389/fnhum.2016.00550
Stephan, K.E., Penny, W.D., Daunizeau, J., Moran, R.J., Friston, K.J., 2009. Bayesian model selection for group studies. NeuroImage 46, 1004–1017. https://doi.org/10.1016/j.neuroimage.2009.03.025
Stevens, J.C., Cain, W.S., 1970. Effort in isometric muscular contractions related to force level and duration. Perception & Psychophysics 8, 240–244. https://doi.org/10.3758/BF03210214
Stoll, F.M., Wilson, C.R.E., Faraut, M.C.M., Vezoli, J., Knoblauch, K., Procyk, E., 2016. The Effects of Cognitive Control and Time on Frontal Beta Oscillations. Cerebral Cortex 26, 1715–1732. https://doi.org/10.1093/cercor/bhv006
Studer, B., Knecht, S., 2016. A benefit–cost framework of motivation for a specific activity, in: Progress in Brain Research. Elsevier B.V., pp. 25–47. https://doi.org/10.1016/bs.pbr.2016.06.014
Tanaka, M., Ishii, A., Watanabe, Y., 2014. Neural effects of mental fatigue caused by continuous attention load: A magnetoencephalography study. Brain Research 1561, 60–66. https://doi.org/10.1016/j.brainres.2014.03.009
Tanaka, M., Ishii, A., Watanabe, Y., 2013. Neural mechanisms underlying chronic fatigue. Reviews in the Neurosciences 24, 617–628. https://doi.org/10.1515/revneuro-2013-0035
Tanaka, M., Sadato, N., Okada, T., Mizuno, K., Sasabe, T., Tanabe, H.C., Saito, D.N., Onoe, H., Kuratsune, H., Watanabe, Y., 2006. Reduced responsiveness is an essential feature of chronic fatigue syndrome: A fMRI study. BMC Neurology 6, 9. https://doi.org/10.1186/1471-2377-6-9
Tanaka, M., Watanabe, Y., 2012. Supraspinal regulation of physical fatigue. Neuroscience and Biobehavioral Reviews 36, 727–734.

https://doi.org/10.1016/j.neubiorev.2011.10.004
Tenenbaum, G., Connolly, C.T., 2008. Attention allocation under varied workload and effort perception in rowers. Psychology of Sport and Exercise 9, 704–717. https://doi.org/10.1016/j.psychsport.2007.09.002
Thorndike, E.L., 1912. The curve of work. Psychological Review 19, 165–194. https://doi.org/10.1037/h0073541
Tobler, P.N., Fiorillo, C.D., Schultz, W., 2005. Adaptive coding of reward value by dopamine neurons. Science 307, 1642–1645. https://doi.org/10.1126/science.1105370
Towal, R.B., Mormann, M., Koch, C., 2013. Simultaneous modeling of visual saliency and value computation improves predictions of economic choice. Proceedings of the National Academy of Sciences of the United States of America 110, E3858–E3867. https://doi.org/10.1073/pnas.1304429110
Townsend, L., Dyer, A.H., Jones, K., Dunne, J., Mooney, A., Gaffney, F., O'Connor, L., Leavy, D., O'Brien, K., Dowds, J., Sugrue, J.A., Hopkins, D., Martin-Loeches, I., Ni Cheallaigh, C., Nadarajan, P., McLaughlin, A.M., Bourke, N.M., Bergin, C., O'Farrelly, C., Bannan, C., Conlon, N., 2020. Persistent fatigue following SARS-CoV-2 infection is common and independent of severity of initial infection. PLOS ONE 15, e0240784. https://doi.org/10.1371/journal.pone.0240784
Tremblay, L., Worbe, Y., Thobois, S., Sgambato-Faure, V., Féger, J., 2015. Selective dysfunction of basal ganglia subterritories: From movement to behavioral disorders. Movement Disorders 30, 1155–1170. https://doi.org/10.1002/mds.26199
Tucker, P., 2003. The impact of rest breaks upon accident risk, fatigue and performance: A review. Work and Stress 17, 123–137. https://doi.org/10.1080/0267837031000155949
Ullsperger, M., Danielmeier, C., Jocham, G., 2014. Neurophysiology of Performance Monitoring and Adaptive Behavior. Physiological Reviews 94, 35–79. https://doi.org/10.1152/physrev.00041.2012
Ullsperger, M., Harsay, H.A., Wessel, J.R., Ridderinkhof, K.R., 2010. Conscious perception of errors and its relation to the anterior insula. Brain Structure and Function 214, 629–643. https://doi.org/10.1007/s00429-010-0261-1
Umemoto, A., Inzlicht, M., Holroyd, C.B., 2019. Electrophysiological indices of anterior cingulate cortex function reveal changing levels of cognitive effort and reward valuation that sustain task performance. Neuropsychologia 123, 67–76. https://doi.org/10.1016/j.neuropsychologia.2018.06.010
Valko, P.O., Bassetti, C.L., Bloch, K.E., Held, U., Baumann, C.R., 2008. Validation of the Fatigue Severity Scale in a Swiss Cohort. Sleep 31, 1601–1607. https://doi.org/10.1093/sleep/31.11.1601
Van Cutsem, J., Marcora, S., De Pauw, K., Bailey, S., Meeusen, R., Roelands, B., 2017. The Effects of Mental Fatigue on Physical Performance: A Systematic Review. Sports Medicine 47, 1569–1588. https://doi.org/10.1007/s40279-016-0672-0
van Dijk, F.J.H., Swaen, G.M.H., 2003. Fatigue at work. Occupational and Environmental Medicine 60, i1–i2. https://doi.org/10.1136/oem.60.suppl_1.i1
van Duinen, H., Renken, R., Maurits, N., Zijdewind, I., 2007. Effects of motor fatigue on human brain activity, an fMRI study. NeuroImage 35, 1438–1449.

https://doi.org/10.1016/j.neuroimage.2007.02.008
Varazzani, C., San-Galli, A., Gilardeau, S., Bouret, S., 2015. Noradrenaline and Dopamine Neurons in the Reward/Effort Trade-Off: A Direct Electrophysiological Comparison in Behaving Monkeys. Journal of Neuroscience 35, 7866–7877. https://doi.org/10.1523/JNEUROSCI.0454-15.2015
Vassena, E., Deraeve, J., Alexander, W.H., 2019. Task-specific prioritization of reward and effort information: Novel insights from behavior and computational modeling. Cognitive, Affective and Behavioral Neuroscience 19, 619–636. https://doi.org/10.3758/s13415-018-00685-w
Vassena, E., Deraeve, J., Alexander, W.H., 2017. Predicting Motivation: Computational Models of PFC Can Explain Neural Coding of Motivation and Effort-based Decision-making in Health and Disease. Journal of Cognitive Neuroscience 29, 1633–1645. https://doi.org/10.1162/jocn_a_01160
Vassena, E., Silvetti, M., Boehler, C.N., Achten, E., Fias, W., Verguts, T., 2014. Overlapping neural systems represent cognitive effort and reward anticipation. PLoS ONE 9, e91008. https://doi.org/10.1371/journal.pone.0091008
Verguts, T., Vassena, E., Silvetti, M., 2015. Adaptive effort investment in cognitive and physical tasks: a neurocomputational model. Frontiers in Behavioral Neuroscience 9, 57. https://doi.org/10.3389/fnbeh.2015.00057
Vogt, B.A., Pandya, D.N., 1987. Cingulate cortex of the rhesus monkey: II. Cortical afferents. Journal of Comparative Neurology 262, 271–289. https://doi.org/10.1002/cne.902620208
Vøllestad, N.K., 1997. Measurement of human muscle fatigue. J Neurosci Methods 74, 219–227. https://doi.org/10.1016/S0165-0270(97)02251-6
Walton, M.E., Kennerley, S.W., Bannerman, D.M., Phillips, P.E.M., Rushworth, M.F.S., 2006. Weighing up the benefits of work: Behavioral and neural analyses of effort-related decision making. Neural Networks 19, 1302–1314. https://doi.org/10.1016/j.neunet.2006.03.005
Warm, J.S., Parasuraman, R., Matthews, G., 2008. Vigilance Requires Hard Mental Work and Is Stressful. Human Factors 50, 433–441. https://doi.org/10.1518/001872008X312152
Weir, J.P., Beck, T.W., Cramer, J.T., Housh, T.J., 2006. Is fatigue all in your head? A critical review of the central governor model. British Journal of Sports Medicine 40, 573–586. https://doi.org/10.1136/bjsm.2005.023028
Wessely, S., 2001. Chronic fatigue: Symptom and syndrome. Annals of Internal Medicine 134, 838–843. https://doi.org/10.7326/0003-4819-134-9_part_2-200105011-00007
Westbrook, A., Braver, T.S., 2016. Dopamine Does Double Duty in Motivating Cognitive Effort. Neuron 89, 695–710. https://doi.org/10.1016/J.NEURON.2015.12.029
Westbrook, A., Braver, T.S., 2015. Cognitive effort: A neuroeconomic approach. Cognitive, Affective, & Behavioral Neuroscience 15, 395–415. https://doi.org/10.3758/s13415-015-0334-y
Westbrook, A., Frank, M., 2018. Dopamine and proximity in motivation and cognitive control. Current Opinion in Behavioral Sciences 22, 28–34. https://doi.org/10.1016/j.cobeha.2017.12.011

Westbrook, A., Kester, D., Braver, T.S., 2013. What Is the Subjective Cost of Cognitive Effort? Load, Trait, and Aging Effects Revealed by Economic Preference. PLoS ONE 8, e68210. https://doi.org/10.1371/journal.pone.0068210
Westbrook, A., Lamichhane, B., Braver, T., 2019. The Subjective Value of Cognitive Effort is Encoded by a Domain-General Valuation Network. The Journal of Neuroscience 39, 3934–3947. https://doi.org/10.1523/JNEUROSCI.3071-18.2019
Westbrook, A., van den Bosch, R., Määttä, J.I., Hofmans, L., Papadopetraki, D., Cools, R., Frank, M.J., 2020. Dopamine promotes cognitive effort by biasing the benefits versus costs of cognitive work. Science 367, 1362–1366. https://doi.org/10.1126/science.aaz5891
Williamson, J.W., Fadel, P.J., Mitchell, J.H., 2006. New insights into central cardiovascular control during exercise in humans: a central command update. Experimental Physiology 91, 51–58. https://doi.org/10.1113/expphysiol.2005.032037
Wilson, C.R.E., Vezoli, J., Stoll, F.M., Faraut, M.C.M., Leviel, V., Knoblauch, K., Procyk, E., 2016. Prefrontal Markers and Cognitive Performance Are Dissociated during Progressive Dopamine Lesion. PLoS Biology 14, 1–31. https://doi.org/10.1371/journal.pbio.1002576
Winstanley, C.A., Floresco, S.B., 2016. Deciphering Decision Making: Variation in Animal Models of Effort- and Uncertainty-Based Choice Reveals Distinct Neural Circuitries Underlying Core Cognitive Processes. Journal of Neuroscience 36, 12069–12079. https://doi.org/10.1523/JNEUROSCI.1713-16.2016
Wittmann, M.K., Fouragnan, E., Folloni, D., Klein-Flügge, M.C., Chau, B.K.H., Khamassi, M., Rushworth, M.F.S., 2020. Global reward state affects learning and activity in raphe nucleus and anterior insula in monkeys. Nature Communications 11, 3771. https://doi.org/10.1038/s41467-020-17343-w
Wylie, G.R., Genova, H.M., DeLuca, J., Dobryakova, E., 2017. The relationship between outcome prediction and cognitive fatigue: A convergence of paradigms. Cognitive, Affective, & Behavioral Neuroscience 17, 838–849. https://doi.org/10.3758/s13415-017-0515-y
Yoshimi, K., Naya, Y., Mitani, N., Kato, T., Inoue, M., Natori, S., Takahashi, T., Weitemier, A., Nishikawa, N., McHugh, T., Einaga, Y., Kitazawa, S., 2011. Phasic reward responses in the monkey striatum as detected by voltammetry with diamond microelectrodes. Neuroscience Research 71, 49–62. https://doi.org/10.1016/j.neures.2011.05.013
Zizzo, D.J., 2010. Experimenter demand effects in economic experiments. Experimental Economics 13, 75–98. https://doi.org/10.1007/s10683-009-9230-z