**Final Report**

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**Date**: 7th November 2017

**Title of Project**: Computational mechanisms of fatigue in Parkinson’s disease

***Summary****:*

*Background*

Fatigue is pervasive across all medical specialities, and is particularly common and debilitating in Parkinson’s disease. It can be experienced in both the cognitive and physical domains, and is associated with profound disruption of daily function. Despite its prevalence and impact, fatigue remains ill-defined and poorly understood. Furthermore, the objective evaluation of fatigue in clinical practice is challenging because of numerous confounding factors that can impair its assessment (e.g., depression). The goals of this research were to develop a methodology that is able to objectively quantify both physical and cognitive fatigue in Parkinson’s disease, in order to identify the shared and separate neural mechanisms that may underlie fatigue in each domain. The general approach was to combine techniques in the related fields of computational modelling, neuroeconomics and cognitive neuroscience, to measure the dynamic effect of fatigue accumulation on individuals’ willingness to exert effort in return for reward.

This study tested the hypothesis that the pathological fatigue experienced by patients with Parkinson’s disease is fundamentally a motivational disorder, in which the costs of exerting effort outweigh the subjective value of continuing on a given course of action in pursuit of a reward. The broad approach was to apply a neuroeconomic framework that has proven to be highly effective in dissecting the neural correlates of motivation. Based on this framework, motivation is characterised as a series of cost-benefit decisions, in which the rewards associated with acting are devalued by the effort that must be exerted. Recently a number of studies have suggested that patients with Parkinson’s disease are less willing to exert effort to obtain rewards (Chong et al. (2015). Cortex). However, it is unclear whether or how fatigue might lead to changes in the willingness to exert effort over time.

*Findings*

In this study, we developed a novel cost-benefit decision-making task in which participants made choices about whether they would rather ‘work’ and exert a level of effort (grip force) for high rewards, or ‘rest’ and exert no effort for a low reward. Using computational modelling approaches, we parameterised fatigue accumulation according to three factors:

(1) The short-term effect of fatigue, which is the result of increased effort exertion in recent trials. A characteristic of this short-term fatigue is that it improves with short periods of rest;

(2) The long-term effect of fatigue, which is the result of accumulated effort exertion over the course of the entire experiment. A characteristic of this long-term fatigue is that it does not improve with short periods of rest; and

(3) The total amount of effort exerted over time.

We then asked which combinations of these parameters accounted for fatigue accumulation in patients with Parkinson’s disease and in healthy individuals.

Thus far, our results indicate that patients with Parkinson’s disease show a specific pattern of fatigue-related deficits compared to healthy age-matched controls. Although fatigue in both the patient and control groups was responsive to rest, there were two key differences. First, short-term Parkinsonian fatigue recovered at a slower rate compared to healthy age-matched controls. In addition, however, there was greater accumulation of long-term fatigue in patients with Parkinson’s disease relative to controls. A hallmark of Parkinsonian fatigue therefore seems to be greater accumulation of fatigue in *both* the short- and long-terms, which is only partially remediable by rest. These data therefore offer a mechanistic basis for the anecdotal observations that rest does not improve subjective fatigue ratings in patients.

*Unanswered Questions*

These data reveal a computational signature of fatigue in PD, by showing that Parkinsonian fatigue is recoverable, but only partially. Having developed this paradigm in the physical domain, we are now following up this result by examining whether these findings are also applicable to fatigue in the cognitive domain. Preliminary data indicate that fatigue across both domains may rely on fundamentally different mechanisms, and that rest may have differential effects on restoring motivation in the cognitive and physical domains. These findings pave the way for understanding the multi-dimensional nature of Parkinsonian fatigue, and the mechanisms that govern it.

*What these research outcomes mean*

This project contributes to our conceptualisation of fatigue theoretically and clinically. In the near term, this methodology could lead to new ways of objectively assessing fatigue in Parkinson’s disease. In addition, we hope to extend our paradigm to a neuroimaging setting, in order to delineate the specific pathways involved in cognitive and physical fatigue. Beyond this project, this methodology has the flexibility to be applied across a multitude of medical conditions, and will lay the foundation for a broader investigation of fatigue across other neurological disorders in which fatigue is a common component (e.g., PD vs stroke vs multiple sclerosis). It is hoped that the outcomes of this project will in turn catalyse the development of new therapies for fatigue, with the methodology developed here providing a sensitive method to monitor treatment efficacy.