

Motivational fatigue:
A neurocognitive framework for the impact of effortful exertion
on subsequent motivation

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This manuscript has been accepted for publication in *Neuropsychologia*'s special issue on
Cognitive Effort on 25 April 2018. The final version will be available under
<https://doi.org/10.1016/j.neuropsychologia.2018.04.030>

Abstract

Fatigue – a feeling of exhaustion arising from exertion – is a significant barrier to successful behaviour and one of the most prominent symptoms in primary care. During extended behaviours, fatigue increases over time, leading to decrements in performance in both physically and cognitively demanding tasks. However, to date, theoretical accounts of fatigue have not fully characterised the neuroanatomical basis of cognitive and physical fatigue nor placed results within broader discussions of the functional properties of the systems implicated. Here, we review recent neurophysiological and neuroimaging research that has begun to identify the neural mechanisms underlying changes in behaviour occurring due to fatigue. Strikingly, this research has implicated systems in the brain, including the dorsal anterior cingulate cortex (dACC), anterior insula and lateral prefrontal cortex, that in separate lines of research have been linked to motivating the exertion of effort, to persisting towards goals and to processing one's internal states. Here, we put forward a neurocognitive framework for fatigue and its impact on motivation. Levels of fatigue arising from effortful behaviours impact on processing in systems that weigh up the costs and benefits of exerting effort. As a result, as levels of fatigue rise, the value of exerting effort into a task declines, leading to reductions in performance. This account provides a new framework for understanding the effects of fatigue during cognitively and physically demanding tasks as well as for understanding motivational impairments in health and disease.

Keywords: Motivation; Effort; Fatigue; Cognitive; Physical; Anterior cingulate

1. Introduction

Trait fatigue – a persistent feeling of exhaustion – is one of the most common symptoms across a broad range of neurological and psychiatric disorders and is the cause of as much as 10% of primary care appointments (Chaudhuri and Behan, 2004; Cullen et al., 2002; Demyttenaere et al., 2005; Skapinakis et al., 2003). It is also present in a milder form in otherwise healthy people, with about 25% of people reporting themselves as being fatigued most of the time. Fatigue is classically thought to arise through effortful exertion and decline through rest. In the most severe cases, no amount of rest is able to ameliorate the feelings of exhaustion. One of the greatest impacts on behaviour is that it leads to persistent and pervasive reductions in daily activity. Similarly, people can experience *state fatigue*, that waxes and wanes during behaviours that require extended periods of cognitive control or motor output, typically impacting on the speed, accuracy or force of behaviours. It also putatively comes with a spectrum of internal changes within the body and neutrally, with marked changes to the autonomic (e.g. cardiovascular) system (Boksem and Tops, 2008; Carroll et al., 2017; Chaudhuri and Behan, 2004; Fairclough and Mulder, 2011; Kurzban et al., 2013; Micklewright et al., 2017).

Strikingly, the same phenomenological experience of fatigue can occur when exerting effort into very different acts. Physically effortful tasks with minimal cognitive demands or cognitively effortful tasks with minimal physical costs both induce a similar feeling of fatigue (Krupp et al., 1989). However, to date there have been few neurocognitive frameworks put forward for fatigue that can account for its multidimensional nature, for why very different behaviours can induce this same phenomenology, and for why it has such dramatic impacts

on task performance.

Here, we put forward a neurocognitive account of the multidimensional nature of fatigue and how it impacts on motivation. We review and integrate behavioural, neurophysiological and neuroimaging experiments examining how performance changes over time due to effortful exertion alongside research examining the neuroanatomical basis of motivation, persistence, performance monitoring and interoception. In doing so, we point to the neurocognitive mechanisms underlying the effects of state fatigue on motivation and task performance (Boksem and Tops, 2008; Hockey, 2011; Kurzban et al., 2013; Tanaka and Watanabe, 2012). We highlight that fatigue arises in circuits involved in executing cognitively and physically demanding tasks, but the integration of these fatigue levels into the information processed in systems that motivate behaviours leads to subsequent drops in the willingness to exert effort. The result of such drops in motivation is reduced vigour and task performance. Although focused on these changes in state fatigue and fatigability within tasks, we briefly outline how this framework may also be linked to accounts of pathological forms of fatigue.

2. Behavioural impacts of physical and cognitive fatigue

2.1 Time-on-task effects for physical or cognitive demands

Perhaps the best characterised feature of fatigue is that it leads to reductions in task performance. Often, such time-on-task effects are used as the defining feature of fatigue, rather than its phenomenology (Boksem et al., 2005; 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 studies 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).

Such time-on-task effects are also present in studies using physical exertion (Marcora, 2009; Meyniel et al., 2014; Tanaka and Watanabe, 2012). This includes studies requiring participants to execute physical force (e.g. grip force) as well as studies examining exercise 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).

Thus, performing tasks that tax cognitive or motor processes over time can both lead to decrements in performance.

2.2 Fatigue: Induced by effort, but restored by incentives and rest

The time-on-task effects of cognitive and physical fatigue also share the common feature of depending on the level of difficulty required in a task. A greater degree of difficulty in a cognitive task (e.g. greater cognitive load or more difficult perceptual discrimination) may

lead to more rapid declines in performance (Boksem and Tops, 2008; Mackworth, 1964; Warm et al., 2008). Similarly, when sustained maximal grip forces are required, the energisation and output of muscles declines (Enoka et al., 2011; Marcora, 2009; Vøllestad, 1997). When submaximal forces, i.e. only a proportion of the maximal force an individual is able to produce, are required, there is less of a decline in muscle output, but there is a concomitant increase in how effortful people perceive the actions to be and in levels of fatigue (de Morree et al., 2014; Marcora, 2009). The finding that increased difficulty induces faster drops in performance – and increases in the perception of effort – raises the possibility that it is the effort exerted into difficult tasks, rather than simply the time spent during the task, that leads to the feeling of fatigue.

Although performance generally tends to decline throughout effortful exertion, incentives and short rests can somewhat counteract fatigue in both the physical and cognitive domains (Boksem and Tops, 2008; Carroll et al., 2017; Marcora, 2009; Meyniel and Pessiglione, 2014). In a modified version of the Simon task – a task examining the effects of the congruency of locations of stimuli and responses – Boksem et al. (2006) demonstrated improvements in performance when fatigued and the partial overcoming of time-on-task effects when participants were told late into the experiment that the best performing subjects would be paid a greater financial reward. Similarly, in a prolonged n-back task, 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 (Hopstaken et al., 2015), 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. Rests of course have similar effects in cognitive

tasks, formally demonstrated across a range of psychomotor and vigilance tasks (Helton and Russell, 2015; Mackworth, 1964) and also illustrated by the common practice of giving people rests. In tasks examining physical grip force, the duration for which people will work and exert effort also depends on incentives and rests. When more rewards are on offer, people work for longer periods of time, and brief periods of rest are enough to restore people to exerting effort again (Meyniel et al., 2014, 2013; Meyniel and Pessiglione, 2014).

Thus, it seems that performance decrements in tasks occur more rapidly if the efforts exerted were greater, and they are also under the influence of brief periods of rest and the incentives on offer.

2.3 Domain-general effects of effortful exertion

Why does performance decline over time in both the physical and cognitive domains? It has been argued that repeatedly performing the same cognitive operations during a task leads to fatigue. Within such an account, performance declines would be due to a reduced capacity of the systems to continue to perform cognitive operations at the same efficacy (See Section 4.4 on potential mechanisms). However, whilst this could plausibly explain why performance declines within a particular task, it cannot account for how performance in one task can affect behaviour in another that relies on distinct processes.

Indeed, there is an abundance of evidence that performing a demanding cognitive task influences subsequent performance on a cognitively or physically demanding task (Inzlicht and Schmeichel, 2012; Van Cutsem et al., 2017). Much of this research has been examining the debated concept of *ego depletion*, i.e. the idea that a limited inner resource is quickly

depleted when exerting self-control over time (see Inzlicht and Schmeichel, 2012, for review and discussion). Yet, there are other studies that have looked at effects of prolonged cognitive task performance on performance in a subsequent cognitive task and that have not explicitly interpreted their results in terms of a depletion of a physical resource (Shigihara et al., 2013). A frequently reported result of these studies are decreases in performance in the second task after having completed an effortful preceding first task, compared to having completed a less effortful first task. While various mechanisms underlying or contributing to these effects have been discussed elsewhere (e.g., Inzlicht and Schmeichel, 2012; Shenhav et al., 2017), above all this suggests that at least some common processes are involved and affected over time. In another study, Blain et al. (2016) examined choices on a temporal discounting task over a whole day of performing a demanding working memory task. Intriguingly, they found a shift in people's valuation of delayed rewards in that they more and more favoured smaller, immediate rewards over larger, delayed rewards. Overall, the fact that extended effortful exertion on one task can impact performance on another suggests that the effects of fatigue may impact on some domain-general processes, even if one assumes that there is not a pool of resources that impact self-control as implied by ego depletion accounts.

Thus, it seems that changes must also occur due to fatigue impacting on motivation. This could be either directly due to changes in systems that motivate behaviour, or due to systems involved in motivation being connected to and under the influence of systems that become fatigued through repeated exertion or stimulation.

3. Motivational fatigue: Effort induces fatigue, impacting subsequent cost-benefit evaluations

Here, we argue that motivation is a domain-general process that is modulated by fatigue (**Fig. 1**). Motivation is often characterised as being underpinned by cost-benefit evaluations, with effort costs having a considerable impact on people's motivation and levels of activity. Theoretically it is argued that effort costs serve to discount the value of rewards and thus their invigorating and incentivising effects (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., 2017; Shenhav et al., 2013; Studer and Knecht, 2016; Verguts et al., 2015; Westbrook et al., 2013). Such valuations are highly subjective and are dependent on how effortful people perceive possible actions to be. When less motivated, people devalue rewards to a greater degree than when motivated (see **Fig. 1b** for an example of how rewards are discounted by physical effort).

In our framework, fatigue increases as effort is exerted and partially decreases with rest, with higher levels of effort increasing the rate of fatigue build-up (**Fig. 1a**). We argue that as levels of fatigue rise, people's weighting of effort costs increases such that efforts previously ascribed high value now transition to a lower subjective value and motivation declines (**Fig. 1b**). As a result, performance decreases.

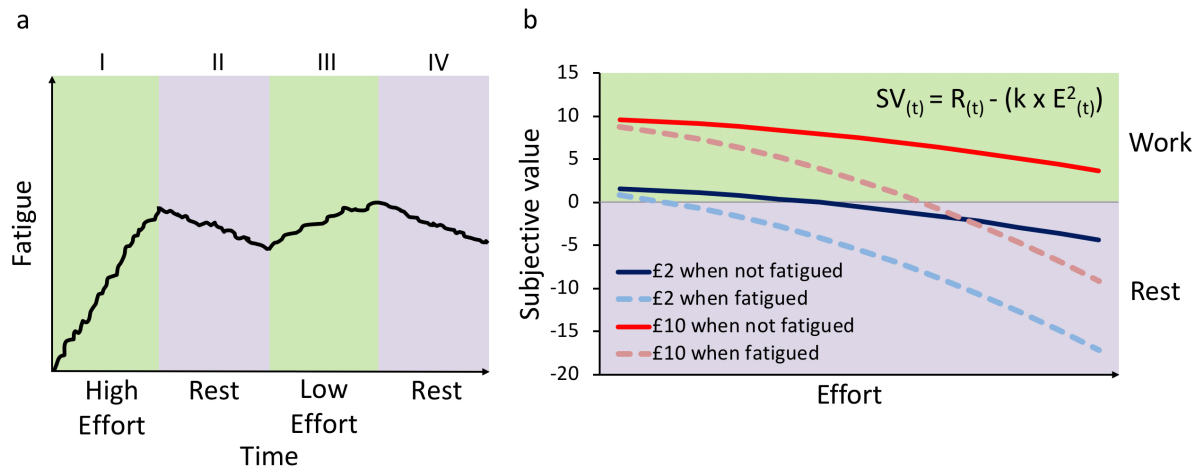


Fig. 1. Proposed mechanisms underlying motivational fatigue. The willingness to exert effort is dependent on the recent history of effortful exertion. (a) Predicted effects of effortful exertion (and rests) on fatigue over the course of a task. Fatigue increases as effort is exerted (I and III) and decreases with rests (II and IV). Higher levels of effort increase the rate of fatigue build-up (see I versus III); (b) Predicted effects of fatigue on subsequent motivation. 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 has provided evidence for a parabolic model of (physical) effort discounting (Chong et al., 2017; Hartmann et al., 2013). Fatigue 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".

3.1 Motivational fatigue under control theoretic principles

Such an account – that exerting effort makes subsequent acts become more effortful – can easily be subsumed under control theoretic principles. In control theory, costs are overcome by the execution of an appropriate intensity control signal (Kurzban et al., 2013; Manohar et al., 2015; Shenhav et al., 2017). The intensity of this control signal can serve to increase the gain or signal-to-noise ratio in a region, allowing it to process information appropriately. If fatigue leads to a greater "cost" to this process, then a greater intensity control signal would

be required to overcome this cost to simultaneously maintain task performance and the vigour of actions. That is, if exerting effort subsequently leads to a greater cost to performing the same processes, the increased cost will devalue rewards further when deciding whether to engage in a behaviour. As a result, when fatigued one would be less willing to engage in the effortful acts that were previously considered “worth it”. The greater intensity – or increased effort – that would be required to maintain performance can therefore only be achieved by greater extrinsic reward (e.g. “I will keep working if you give me more money”) or an internal “motivational boost” (“You can do this, keep going”) (see also Job et al., 2010; Miller et al., 2012, for how people’s individual general beliefs about the effects of exertion might be related to their sustained cognitive performance).

4. Systems in the brain that fatigue through cognitive and physical effort

As outlined below, fatigue arises as a function of effortful exertion within circuits that are recruited during a cognitive or physical task. However, the connections from these systems to areas that guide motivated behaviour presumably lead to their internal states being weighed into decisions of whether it is worth exerting effort to obtain subsequent rewarding benefits (**Fig. 2**). As such, fatigue leads to a drop in the value ascribed to exerting subsequent efforts relative to pursuing alternative courses of action (Boksem and Tops, 2008; Hockey, 2011; Kurzban et al., 2013).

The account we propose suggests that as fatigue increases, overcoming the increased costs would require a greater intensity control signal, thereby further devaluing the rewards associated with acting. When performance is still maintained, activity in task-related areas

and in areas involved in motivation should therefore increase. 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. In the next sections, we highlight the systems in the brain that show changes in activation during tasks that might be linked to fatigue. We do this separately for cognitively and physically demanding tasks to highlight overlapping and distinct systems.

4.1 Physical fatigue

Studies probing physical fatigue have used functional Magnetic Resonance Imaging (fMRI), Positron Emission Tomography (PET) and Electroencephalography (EEG) to identify the systems in the brain in which neural activity parallels such behavioural changes. Strikingly, three systems emerge across studies as showing changes in BOLD signal, in regional Cerebral Blood Flow (CBF) and in event-related potentials (ERPs). Note that in this section we synthesise a large number of studies, for more detailed, specific reviews see the work of Marcora (2009), Tanaka and Watanabe (2012) and Williamson et al. (2006).

Firstly, studies show that during sustained exertion or when examining pre and post physical fatigue inducing tasks, there are changes in motor and sensorimotor systems. This includes changes in CBF and BOLD signals in the primary motor cortex, premotor cortex and the supplementary and pre-supplementary motor areas, and changes in EEG components that arise 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). In one Magnetoencephalography (MEG) study, Meyniel and Pessiglione (2014) aimed specifically 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 studies have also shown that signals from premotor and motor areas are linked to increases in the perception of physical effort during fatigue inducing tasks (de Morree et al., 2014; Marcora, 2009). It would therefore seem that increases in the effort required to exert force when physically fatigued are linked to altered responses in sensorimotor systems.

Secondly, there are changes in activity 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 exteroceptive signals from the muscles and interoceptive bodily signals (Liu et al., 2002; Meyniel et al., 2013; Tanaka and Watanabe, 2012). For example, Meyniel and colleagues used MEG and fMRI to examine how people choose to take rests as a function of the effort they have exerted across a certain time interval during which a continuous force is required to obtain rewards, and to examine whether signals in any brain region might track levels of fatigue. 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 (Meyniel et al., 2013). Posterior portions of the insula therefore have signals that mimic the trajectory that feelings of fatigue would be expected to have during physical exertion and rest.

Finally, perhaps the most consistent finding across all of the studies outlined above is that there are additional changes in activity in areas that are more strongly linked to motivation and cognitive control (see Section 5). 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), although it has also been suggested that error signals in cognitive tasks may co-localise with midcingulate motor areas (Amiez et al., 2013; Procyk et al., 2016). However, a large number of studies examining fatigue find activity in regions lying clearly rostral and anterior to this, regions that through their anatomical properties are more likely to be involved in cognitive processing (Haber and Knutson, 2010; Parent and Parent, 2006). Studies using either EEG or fMRI have shown changes in anterior portions of the midcingulate cortex (MCC)/anterior cingulate sulcus (ACC; area 24c'/32'), the anterior portions of the insula (AI; area idg), and portions of DLPFC putatively in areas 46 and 9/46 (Liu et al., 2002; Marcora, 2009; Tanaka and Watanabe, 2012). This suggests that there are changes in activity beyond the motor system that can be linked to an increased perception of fatigue. 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).

These findings demonstrate that behavioural outputs and the perception of effort related to fatigue lead to changes in two separate systems that process interoceptive and exteroceptive signals and are directly linked to the physical exertion, as well as in a third system that – as will be outlined below – is more strongly linked to motivation and cognitive control.

4.2 Cognitive fatigue

Studies examining the neural mechanisms underlying cognitive fatigue have used a variety of cognitive tasks and looked for correlates of changes in performance. Much like in tasks requiring physical exertion, a common theme is that there are systems that show changes in activity that appear to relate to the specific task or cognitive operations. Studies that require sustained attention, for instance, show decreased activity in lateral frontal and parietal areas that 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). Results from studies using different tasks do show considerable variability in terms of the areas of the brain involved. However, there is certainly evidence that areas thought to play important roles in the cognitive operations important for the respective tasks show changes over time that are linked to changes in the perception of effort and fatigue.

Perhaps the most consistent finding in research examining changes in neural activity with cognitive fatigue is that there are also changes in the same areas as those that change with physical fatigue – areas that have been linked to motivation (see Section 5). 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 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). Similarly, 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). Relatedly, in a working memory task, signs and feelings of fatigue were correlated with activity in dACC and pre-supplementary motor area as assessed by fMRI (Wylie et al., 2017). 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). Overall, this literature reveals that exerting cognitive effort is accompanied by decreased performance and neural changes in various cortical areas, particularly in the ACC, insula and DLPFC.

4.3 A domain-general system linked to motivational fatigue

The reported findings suggest that with extended effortful exertion, regardless of whether it is cognitively or physically demanding, declines in performance linked to fatigue are related to changes in activity in several systems that fall into two categories. Firstly, cognitive and physical tasks induce changes in areas 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 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 comprising the dACC, AI and DLPFC that show altered activity across both cognitive and physical tasks. In Section 5, we focus on this second system and highlight how its connectivity and functional properties lead to its likely role in a declining willingness to exert effort into tasks as people become fatigued.

4.4 Neuronal mechanisms of fatigue in task-related areas

Although to date formal accounts of the precise mechanisms underlying fatigue have been scarce, relevant theories for how neurons process information may offer clues for how fatigue arises. Theories of neural coding have tended to focus on how the signal-to-noise ratio (or gain) in populations of neurons needs to be appropriate in order to perform demanding processes, such as a demanding task (Aston-Jones and Cohen, 2005; Heeger, 1992). It is reasonable to assume that attaining the optimal signal-to-noise ratio in a population of neurons could be considered as “effortful”, coming at a cost. How could fatigue arise in such processes? One possibility is that neurons adapt to repeated stimulation (Grill-Spector et al., 2006). Thus, repeatedly performing a cognitive operation or innervating muscles may lead to adaptation. The result would be a change in the signal-to-noise ratio of a population of neurons as fatigue increases (*neuronal fatigue*). Although this is somewhat speculative, if this was the case, then overcoming this reduced signal-to-noise ratio and establishing the appropriate gain in a population of neurons would require greater control. In control theoretic terms this may come only from a greater intensity control signal (Manohar et al., 2015) and possibly from associated increased activity of acetylcholine in respective cortical areas (Sarter et al., 2006). I.e. more effort would be required to get the same output when a population of neurons becomes fatigued.

5. Motivational fatigue: A system that monitors internal states and sustains motivation

Here, we propose that fatigue arises in circuits involved in task performance and that other regions involved in choosing whether to exert effort “monitor” the internal state of task performing regions. The result is a reduction in the willingness to exert effort over time.

Explicitly this account therefore suggests that as fatigue increases in task executing regions, greater input into that region is required to obtain the same output, in the same manner to how a muscle gets fatigued. We argue that this change in how much effort will be required to perform a task is monitored within downstream regions – the Insula, DLPFC and dACC.

Thus, the monitoring of the internal states of task executing regions within this network that is also engaged when choosing to exert effort will serve to amplify the weight given to the costs of exerting effort in subsequent decisions of whether a behaviour is “worth it” (**Fig. 2**).

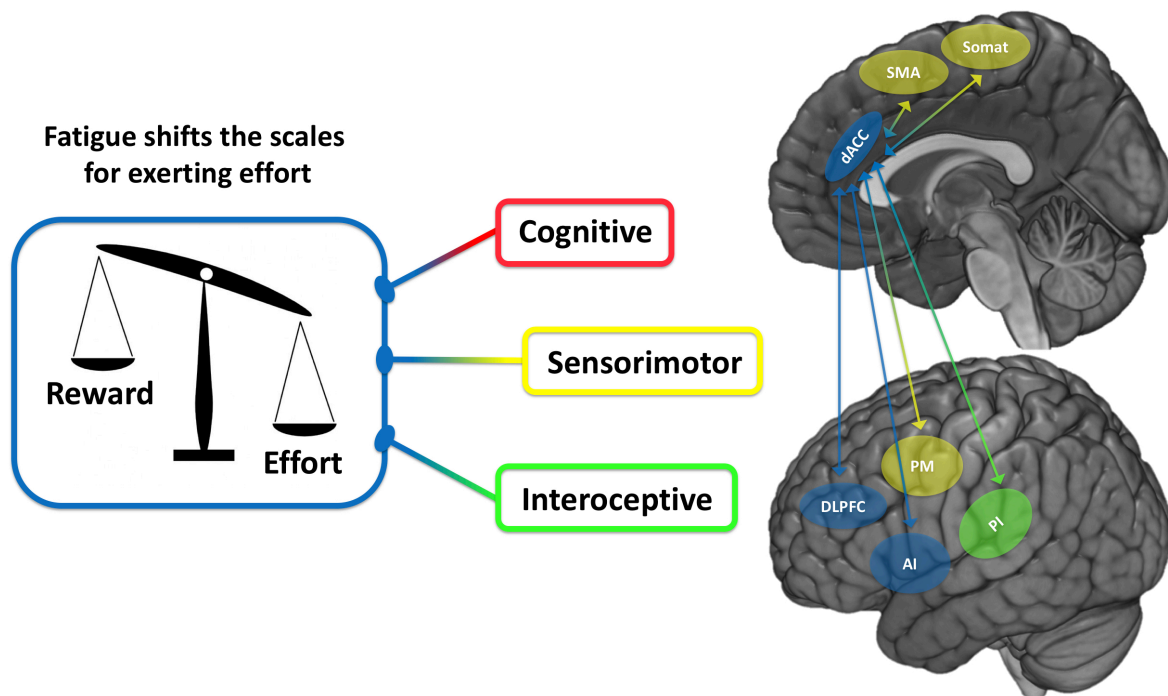


Fig. 2. Proposed systems in the brain underlying motivational fatigue. Fatigue can arise in interoceptive and sensorimotor systems, including but not limited to those highlighted in green and yellow respectively on the brain image, as well as in cognitive areas which are rather distributed across the brain. The dorsolateral prefrontal cortex (DLPFC; areas 46 and 9/46), anterior insula (AI; area idg) and dorsal anterior cingulate cortex (dACC; area 24c'/32') serve as a core circuit evaluating the costs and benefits of exerting effort into behaviours. The connections of DLPFC, AI and dACC to the systems processing interoceptive, sensorimotor and cognitive information (note that not all of the connections are depicted on the brain image) leads fatigue in these systems to increase the weighting of effort costs in subsequent cost-benefit evaluations. As a result, people are less motivated to exert effort, leading to decrements in task accuracy and in the degree to which actions are invigorated. Premotor cortex (PM), supplementary motor area (SMA), somatosensory cortex (Somat), posterior insula (PI).

The anatomical properties of the dACC, DLPFC and insula make them well placed to perform such a function, and indeed they are often considered as a circuit with common functional properties. The most dense projections of area 24c'/32' in the macaque brain are to regions within the DLPFC and to more anterior portions of the insula, and similarly there is evidence of strong anatomical and functional connectivity in humans (Balsters et al., 2016; Neubert et al., 2015; Vogt and Pandya, 1987). Models of these different regions have often arrived at

similar theoretical and computational underpinnings (Alexander et al., 2017a, 2017b; Vassena et al., 2017).

These regions, as multimodal/association cortical areas, also receive broad input from several other systems. This includes parts of the motor system, systems that process interoceptive and exteroceptive information, regions involved in cognitive processing, as well as portions of the basal ganglia that are linked to motivation (Balsters et al., 2016; Craig, 2009; Mesulam and Mufson, 1982; Neubert et al., 2015; Pandya et al., 1981; Petrides and Pandya, 2006; Vogt and Pandya, 1987). What does this suggest about their role in processing the effects of fatigue? This connectivity profile makes them well placed to integrate information about the internal states of a broad range of other systems and suggests a “mediating” role of dACC, DLPFC and AI. If the internal states of systems that perform tasks are susceptible to neuronal fatigue, then information processing within the ACC, DLPFC and insula will be under its influence. In the next sections, we highlight how these regions play crucial roles in guiding decisions of whether it is worth exerting effort, in persisting or switching to different courses of action, and in monitoring the states of other systems. Thus, neuronal fatigue within task-relevant systems may serve to impact on subsequent motivation through the inherently broad range of connections of the dACC, insula and DLPFC.

5.1 Choosing to exert effort to obtain rewards

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 (Le Heron et al., 2017; Westbrook et al., 2013; for recent reviews on the role of dopamine see also Cools, 2015; Salamone et al., 2016; Westbrook and Braver, 2016). The most commonly implicated areas in effort-based decision-making are the ventral striatum (VS), the AI, the DLPFC, as well as interconnected portions of the dACC (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; 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 (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 studies, there is also evidence that the cortical regions involved in choosing to exert 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, even though effort would only be 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, but

parametrically varied the effort 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 was not contaminated by any effects of preparing to exert effort. They found that the DLPFC, insula and dACC all signaled the effort-discounted value of rewards and did so regardless of whether the effort was in the cognitive or physical domain (**Fig. 3a**).

The DLPFC, dACC and AI therefore play crucial roles in motivated behaviour and particularly in choosing whether it is worth exerting efforts. As highlighted in Section 4, activity in these regions also changes with both cognitive and physical fatigue (see also Blain et al., 2016; **Fig. 3d**). Taken together, these results suggest that fatigue would impact on subjective valuations of exerting effort to obtain rewards. This could lead to greater discounting of the rewards associated with performing a cognitively or physically demanding task as fatigue increases, and in turn lead to reductions in performance or force respectively.

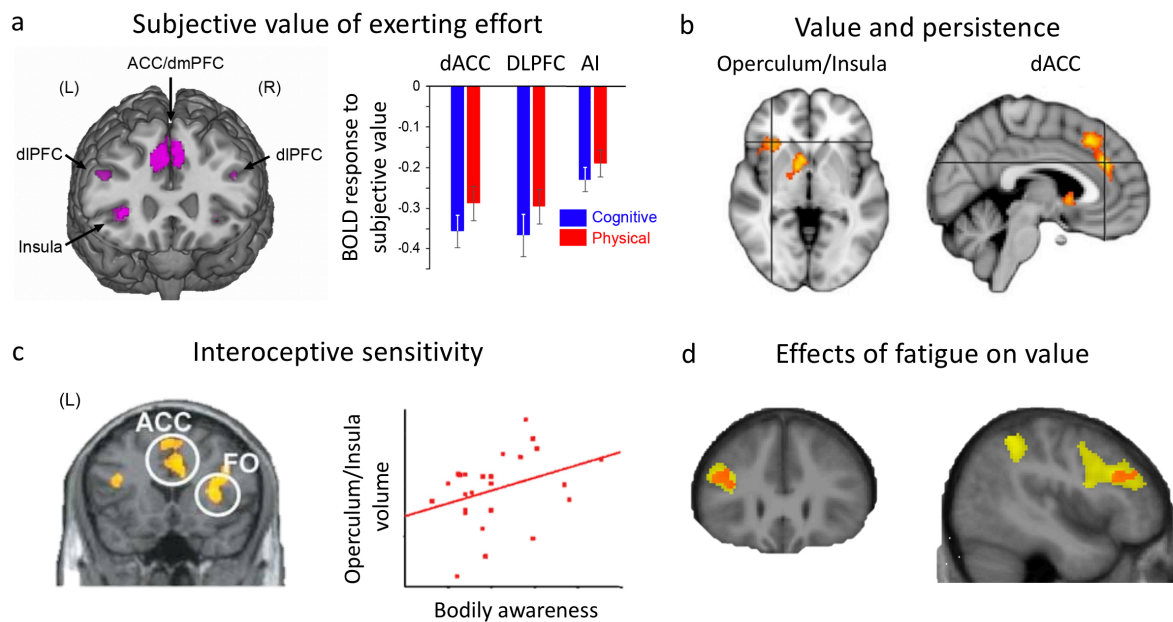


Fig. 3. Overlapping systems for valuation, persistence, interoception and fatigue. (a) Activity in the dorsal anterior cingulate cortex (dACC), dorsolateral prefrontal cortex (DLPFC) and anterior insula (AI) signals the subjective value of exerting effort for rewards, regardless of whether the effort is cognitive or physical (adapted from Chong et al., 2017); (b) Similar regions of the dACC and AI calculate the value of persisting with the current course of behaviour versus switching to an alternative (reprinted from Wittmann et al., 2016); (c) Activity in overlapping regions of the DLPFC, frontal operculum/AI and dACC varies with heartbeat detection ability, and grey matter volume in the AI correlates with individual differences in the ability to detect one's bodily signals (adapted from Critchley et al., 2004, by permission from Springer Nature); (d) The DLPFC signals value in a temporal discounting task, however, signals in this region vary as a function of fatigue during daylong cognitive effort (adapted from Blain et al., 2016, Supporting Information, by permission). Original figures 3a and 3b are licensed under CC BY 4.0.

5.2 Persisting or switching to alternatives

Theoretical accounts have also linked the dACC, AI and DLPFC to persistence and sustaining motivation throughout a task, in order to reach more temporally extended goals (Holroyd and McClure, 2015; Holroyd and Yeung, 2012; Kolling et al., 2016a, 2016b; Umemoto et al., 2017). The dACC in particular has been linked to ascribing value to different courses of action throughout extended sequences of behavior and to “switching” to alternative courses of action when the current course of action no longer has sufficient value.

Stimulation of the dACC leads 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). Wittmann et al. (2016) used a task where participants had to make decisions to persist with the current environment or to switch to an alternative, having monitored the delivery of momentary rewards over an extended time period. Using fMRI they found that within the dACC, activity tracked the history of how rewarding the environment had been, a crucial factor in making the decision of whether to persist or switch. In addition, although not the focus of the study, they also found a similar response in a region lying at the border of the AI and the frontal operculum (**Fig. 3b**). Although not specifically related to fatigue, to how much effort had been exerted or to how much effort participants were willing to exert, it suggests that the dACC and AI are engaged in computing the value of a current course of action relative to others.

How might this relate to fatigue? If fatigue serves as an additional weight to the cost of exerting effort, as it increases, the value of exerting effort to obtain rewards relative to alternative courses of action should decrease (**Fig. 1b**). To overcome increasing effort costs, activity in the AI and dACC would need to be increased to “persist” and for performance to be maintained. When such motivational “boosts” are not possible because the expected rewards no longer outweigh the expected costs of pursuing a particular action, people will “give up” and switch to an alternative course of action that they feel is currently less effortful or more rewarding (e.g. having a meal). Previous accounts have proposed a role for these regions in boosting motivation and increasing performance (Botvinick and Braver, 2015; Umemoto et al., 2017; Verguts et al., 2015). Although not previously demonstrated, we hypothesise that such a boost is necessary specifically to overcome the increased

perception of how effortful behaviour will be when fatigued.

5.3 Interoception, metacognition, and the monitoring of performance

Perhaps less often acknowledged in theoretical accounts of the AI, DLPFC and dACC that focus on motivation is that these regions are also implicated in monitoring “internal states”, albeit in different forms. Such monitoring of internal states highlights them as candidates for monitoring how fatigued systems in the brain are.

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 where the structure and function of the insula correlates with people’s capacity to detect and be aware of their own heartbeats (Ainley et al., 2016; Critchley et al., 2004) (**Fig. 3c**). Other studies 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 an individual is of their errors during cognitive tasks relates 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 levels of fatigue 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 linked to people's sensitivity and ability to detect their own heartbeats (Critchley et al., 2004) (**Fig. 3c**). Further studies suggested a role of the ACC in the conscious perception of effort (Naccache et al., 2005; Williamson et al., 2006).

5.4 A system for monitoring fatigue and choosing whether to carry on

Together, these results suggest that the dACC, insula and DLPFC may monitor internal states of other systems. Based on the connectivity profiles outlined above, 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 levels of fatigue in circuits that are involved in executing effortful tasks. As outlined above, this would lead fatigue to be multidimensional and arise from very different effortful acts that tax cognitive or motor processes. Such integration of current levels of fatigue into the information processed within the dACC, insula and DLPFC could bias choices of whether to put effort into subsequent trials of a task, thereby adjusting behaviour accordingly.

This would explain a broad range of findings across studies which suggests no simple correlation between activity in certain brain regions, levels of fatigue, and performance measures. For example, when fatigue levels increase and reward levels are not adjusted accordingly, activity in task-related brain regions as well as respective value signals in motivation-associated brain regions will decrease, resulting in impaired performance or the selection of an alternative course of action. When the benefits outweigh the efforts, however, activity in motivation-associated brain regions might increase such that activation of the respective task-related systems is maintained at a sufficient level and there is less of a decline in performance. Yet, most studies do not take measures of motivation or direct measures of fatigue but instead use changes in reaction time, vigour or accuracy in a task as a proxy measure. As a result, how the willingness to exert effort and fatigue change over time often cannot easily be disentangled from correlated factors.

Moreover, such proxy measures also do not allow for fatigue to be easily distinguished from other factors such as sleep deprivation, satiety or boredom. In most tasks, these would serve to lead to similar changes in accuracy or vigour. However, our framework would make

the prediction that neither satiety nor boredom would arise from high levels of exertion, even if they lead to similar behavioural outcomes in many tasks. Future research should begin to try and disentangle these processes from each other using direct measures of each, rather than using task accuracy and response vigour under the assumption that they measure fatigue.

6. Motivational fatigue in pathological conditions

6.1 Neurocognitive theories of pathological fatigue

The aim of this review is to highlight the potential mechanisms underlying the impact of fatigue on motivation in terms of its decline over time in healthy people, or state fatigue. However, it is notable that there are links between this account and elements of those that have been proposed to account for the symptoms of fatigue in neurological and psychiatric conditions. Here, we note these links to highlight how understanding motivational fatigue in healthy people and in pathological conditions may be a fruitful joint endeavor.

One recent theory of fatigue 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 suggested fatigue arises in interoceptive systems, through a failure to be able to accurately predict internal bodily states (Stephan et al., 2016). A third, prominent account of fatigue in neurological disorders has highlighted that impairments in the basal ganglia and connected cortical areas, including those highlighted in this review, lead to an increased perception of effort, leading to reduced daily

activity (Chaudhuri and Behan, 2004; see also Dobryakova et al., 2013). Finally, an additional theoretical account suggests that the motivational impairments in pathological fatigue arise due to inflammation (Felger and Treadway, 2017). This is supported by the observations of elevated levels of the pro-inflammatory cytokines interleukin-6 (IL-6) and tumour necrosis factor- α (TNF α) in conditions in which fatigue is highly prevalent (Dowlati et al., 2010), which may lead to heightened levels of fatigue and reduced willingness to exert effort (Draper et al., 2018). This inflammation has been suggested to be linked to reductions in the efficacy of dopaminergic systems, including midbrain projections to portions of frontal cortex that guide effort-based decisions (Le Heron et al., 2017; Salamone et al., 2016).

Strikingly, all four of these theories of pathological fatigue share similarities with the account proposed here for state fatigue. However, in each of these accounts fatigue arises through changes in one system in the brain, either impacting motor, interoceptive, or motivation relevant systems. Here, we suggest that the phenomenology of fatigue can arise through repeated execution of the cognitive or motor processes necessary for a task. As such, the feeling of fatigue could arise through changes in systems underlying motor, interoceptive, or cognitive information processing rather than arise exclusively from one system. Our account may therefore provide novel ways of thinking about pathological fatigue, by highlighting how its phenomenology can lead to motivational impairments through either cognitively or physically demanding tasks.

6.2 Relationship to apathy

Apathy and fatigue are highly correlated in both healthy people and many psychiatric and neurological conditions (Ang et al., 2017; Chaudhuri and Behan, 2004). Furthermore, neurocognitive accounts of apathy have similarly highlighted a reduced willingness to exert effort, linked to the function of similar systems as those we have highlighted as playing a role in state fatigue, including the dACC and VS (Bonnelle et al., 2016, 2015; Hartmann et al., 2013; Le Heron et al., 2017; Lockwood et al., 2017). However, although commonly occurring and sharing the behavioural symptom of reduced daily activity, they are distinguishable. In particular, the phenomenology of fatigue and apathy are distinct, with apathy not characterised by the feelings of exhaustion that are the hallmark of state and trait fatigue (Ang et al., 2017). As a result, people can be apathetic and have lost the will to exert effort, but do not report high levels of exhaustion. In our account, we highlight that this may be due to the fact that the feeling of exhaustion arises due to changes in areas processing information specifically related to a task, whereas the DLPFC, dACC and AI monitor this information. This differs from apathy, for which disruption to the dACC and VS appear to be the primary source of apathetic symptoms and which seems not due to changes specifically in systems that execute tasks (Le Heron et al., 2017).

7. Conclusion

Declines in performance, in terms of accuracy, vigour and force, are hallmarks of physical and cognitive fatigue. In this review, we highlight how such effects of fatigue may be related to changes in systems in the brain that are involved in performing the cognitive or motor operations necessary for performance and how they are monitored by a domain-general

system comprising the dACC, DLPFC and AI. In doing so, we point to how the exertion of effort into a task may lead to a subsequent drop in the willingness to exert effort and the motivation to persist with behaviours over time. This review therefore provides a framework for understanding the functional anatomy underlying state fatigue. Moreover, the proposed framework has the potential for guiding future work examining the neurobiology of fatigue as well as informing work examining trait and state fatigue in health and disease.

Future directions

- What role do neuromodulators linked to the willingness to exert effort, such as dopamine and serotonin, have in motivating extended behaviours over time (see Chong et al., 2015; Meyniel et al., 2016)?
- How is the time course of recovery affected by effort type (cognitive or physical), effort duration, and changes in task-dependent brain systems?
- Are the effects of fatigue on increasing the perception of effort, on decreasing reward sensitivity, or on both, and are these linked to different frontal circuits (see Klein-Flügge et al., 2016)?
- How does motivational fatigue vary dependent on temporally extended goals where rewards are only obtained after multiple actions?
- How closely tied are one's "awareness" of fatigue and its effects on motivation?
- Are the mechanisms underlying state fatigue similar to those underlying pathological fatigue, and which factors contribute to the development of pathological fatigue?

Acknowledgements

MAJA was funded by a BBSRC Anniversary Future Leader Fellowship (BB/M013596/1) and Wellcome Institutional Strategic Support Grant. TM was funded by a scholarship from the German Academic Exchange Service (DAAD).

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