**Cognitive fatigue effects on physical performance: The role of interoception**

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**Abstract**

The consensus of opinion, with regard to the effect of cognitive fatigue on subsequent physical performance, is that there is a small, negative effect but there is no consensus regarding the mechanisms involved. When glucose levels are normal, undertaking cognitive tasks does not induce energy or neurotransmitter depletion. The adenosine hypothesis is questioned as cognitively-induced increases in adenosine release are phasic and transient, while persistent effects of adenosine are tonic. Thus, the most likely explanation for a negative effect of cognitive fatigue would appear to be changes in perceptions of effort, for which there is some evidence from subjective participant feedback, while interoceptive theory would suggest a role for motivation levels. Cognitive and physical fatigue are dependent on interoceptive mechanisms, in particular the interactions between top down predictions of effort from the dorsolateral prefrontal cortex (PFC) to the insula cortex, anterior cingulate cortex, ventromedial and ventrolateral PFC and bottom-up feedback from the lamina I spinothalamic pathway, and the vagal and glossopharyngeal medullothalamic pathway. The dopaminergic mesocorticolimbic and the locus coeruleus-noradrenaline pathways are also vital. It would appear that cognitive fatigue leads to different predictions of the expected sensory consequences of undertaking the exercise than in the control condition and there is some evidence that motivation can overcome this. Much more research, in which motivation levels are manipulated, is necessary as the effects are small and the reasons for cognitive fatigue causing changes in predictions of sensory consequences are not clear.

**Cognitive fatigue effects on subsequent physical performance: The role of interoception**

**1. Introduction**

 Systematic reviews and meta-analyses of the effects of cognitive fatigue on subsequent physical performance have led to somewhat differing conclusions. Van Cutsem et al. [1], in a qualitative, systematic analysis, came to the conclusion that cognitive fatigue does have a significant effect on subsequent physical performance. Interestingly, they found that submaximal endurance performance was impaired, whereas, maximal intensity performance was not, a finding that was supported by Pageaux and Lepers’ narrative review [2]. In a meta-analysis, we [3, 4] found a small but significant mean pooled effect size (g = -0.26) that was slightly greater than the threshold of -0.20, which Cohen [5] sees as trivial regardless of probability level. In a more recent meta-analysis, Brown et al. [6] demonstrated a slightly larger, but still small, significant mean pooled effect size (g = -0.38). They also supported the narrative reviews by demonstrating significant effects for isometric resistance (g = -0.57), dynamic resistance (g = -0.51) and submaximal aerobic exercise (g = -0.26), but no significant effect for maximal anaerobic performance (g = 0.10).

 The differences between the results of Brown et al. [6] and ourselves [3,4] maybe due to the different criteria for inclusion in the two analyses. Moreover, we examined only within-subject designs, while Brown et al. also included between-subject studies. Their examination of a within-subject design sub-group found a mean pooled effect size of g = -0.30, which is not much different to that which we demonstrated. However, a between subjects sub-group demonstrated a medium mean pooled effect size (g = -0.66). One might question the use of between-subject designs for such studies, as results may be affected by inter-individual differences. Arguably the most important difference in the two meta-analyses is that Brown et al. utilized cognitive tasks ranging from ~4 min to 90 min in duration, while we had only one study of < 30 mins, yet Brown et al. showed the larger pooled effect size. This counterintuitive difference between short and long cognitive performance is discussed in section 4, with particular reference to Craig’s [7] theory of interoception.

 The meta-analyses and narrative reviews outlined above support some effect, albeit small, of cognitive fatigue on subsequent physical performance. However, there are major issues in deciding which mechanisms are involved. In particular, issues arise from why submaximal aerobic and resistance exercise should show large effects but maximal performance (i.e. covering a given distance in as fast a time as possible; covering as much distance as possible in a given time; with resistance exercise, maintain a given force production to failure/exhaustion; completing as many repetitions as possible in a given time, or completing as many repetitions as possible before voluntary exhaustion, but not maximal intensity anaerobic performance), small and maybe non-significant effects. Also, the issue of short versus long duration cognitive tasks needs addressing. In this opinion article, I outline mechanisms within the interoceptive system, particularly the role of catecholamines [7], which I believe may explain the conclusion suggested by the reviews and provide scope for future research.

**2. Brain metabolism during cognition**

 It has been argued that cognitive fatigue, as a result of undertaking tasks designed to induce ego depletion or mental fatigue, lowers energy supplies to the brain [8, 9] and may deplete neurotransmitter concentrations [10, 11]. We have contested this elsewhere [3] and recently Martin et al. [12] also repudiated this claim. Brain metabolism is dependent on blood-borne glucose being transported across the cerebral vascular endothelial cells. It is generally thought that in healthy human beings, during normoxia, normothermia and normoglycemia, these processes result in the production of ample adenosine triphosphate [13, 14]. There is very little difference between brain metabolic rates when humans are completely passive and resting, and when they are observably doing something [15], as demonstrated by activation of the default mode network [16]. Generally, brain glucose only becomes rate limiting during hypoglycemia [17], therefore it is very unlikely that in the protocols utilized in the cognitive fatigue research, brain metabolism broke down due to inadequate glucose supply. However, this does not cover neurotransmitter supply.

 Of importance in the cognitive fatigue studies are the neurotransmitters dopamine and noradrenaline. These are particularly important in the neural pathways involved in cognition and reward/motivation [18, 19]. However, there is little likelihood that cognitive activity for ≤ 90 minutes (the durations used in most of the reviewed studies) would negatively affect catecholamines concentrations. The precursor of catecholamines synthesis is the aromatic amino acid tyrosine. It is plentiful in a normal diet and can be formed in the liver by the hydroxylation of phenylalanine [20]. Tyrosine is transported across the blood-brain barrier by the facilitative transporter L1 [21] and the process of synthesizing dopamine and noradrenaline is undertaken. Tyrosine hydroxylase (TH), which is encoded by the TH messenger ribonucleic acid gene, is the rate-limiting enzyme in the whole process [20]. It would appear that to induce brain energy and/or catecholamines depletion will require considerably longer than 90 mins [22]. However, such interpretation does not cover the claims of Pageaux and colleagues [23-25] and Martin et al. [12], who pointed to cognition-induced build up of extracellular adenosine in the anterior cingulate cortex (ACC) leading to increased perception of effort in the subsequent exercise.

 Adenosine modulates dopaminergic activation in order to maintain homeostasis between energy supply and uptake. As tonic dopamine concentrations increase linearly with activation, so do extracellular adenosine levels. High concentrations of adenosine inhibit dopamine synthesis and release. However, increases in adenosine due to activation of dopamine neurons during cognitive tasks designed to induce ego depletion or cognitive fatigue is phasic not tonic and has been shown to be induced when dopamine is released phasically [26, 27]. Phasic release of dopamine is induced by cognition but only when tonic concentrations of dopamine are of moderate levels. High tonic concentrations of dopamine inhibit phasic release of dopamine [28]. Moreover, phasic release of adenosine is transient and it is quickly removed by reuptake and conversion to adenosine monophosphate or by degradation to inosine, hence a lack of a build-up of extracellular adenosine in the brain [27, 29]. However, one can not write off possible effects of adenosine because research has been conducted with rodents and generally demonstrates the effect of increases in extracellular adenosine concentrations over the full waking period [30] or uses application of adenosine agonists to induce concentrations of pathological levels similar to those found in ischemia or anoxia [30, 31].

 Research with humans that examines the time it takes for undertaking cognitive tasks to significantly increase tonic release of adenosine is needed but difficult to do. Judging by the rodent research, it will be over long periods of time and induce tonic release of adenosine, activating A2A receptors which inhibit dopamine D2 receptors thus decreasing motivation [32]. Phasically released dopamine induces activation of A1 adenosine receptors [33-35], and maintains homeostasis. Caffeine, an antagonist of adenosine, has demonstrated facilitation of simple cognitive tasks, e. g simple and choice reaction time, but not executive functions [36], which are thought to underly ego depletion [37]. Moreover, caffeine also has effects on noradrenaline, acetylcholine and 5-hydroxytryptamine, which will affect arousal levels and hence facilitate simple cognitive tasks (e.g. simple and choice reaction time) [38]. Therefore, it is difficult to support the claims that transient increases in extracellular adenosine causes cognitive fatigue.

**3. Interoception during exercise and cognition**

 In this section, the role of the interoceptive system during exercise and cognition is briefly outlined (see Figure 1), for more detail see [39]. Prior to the commencement of activity, the dorsolateral (DL) prefrontal cortex (PFC) feeds forward to the anterior insula cortex (AIC) a prediction of the expected sensory feedback [7]. During activity, small-diameter Aδ- and C-type primary afferent fibers, which sense the physiological condition of all tissues of the body, relay afferent information in the lateral spinothalamic tract to the main homeostatic integration sites in the brainstem. The homeostatic integration sites also receive vagal and glossopharyngeal afferent feedback via the nucleus tractus solitarii (NTS). The feedback includes information concerning a wide variety of physiological conditions [7, 40]. Both the lamina Ⅰ lateral spinothalamic and NTS medullothalamic axons terminate in the posterior and basal parts of the ventral medial nucleus of the thalamus, which project to the AIC [7].

*Insert Figure 1 about here*

 Bottom-up afferent information received by the insula cortex is mapped firstly in the contralateral AIC and then, by way of a callosal pathway, a lateralized, second-order re-representation is made on the right AIC [40]. This becomes consciously accessible. The AIC also receives afferent input from the somatosensory cortex [41]. The AIC compares the feedback with the top-down predictions of interoceptive state, which it received from the DLPFC, allowing the individual to make a subjective, affective perception of their physiological and emotional state. This is forwarded to the ACC, ventromedial (VM)PFC and lateral (L)PFC [7, 41].

 The AIC and ACC have bidirectional projections with the VMPFC, which also has connections with the amygdala, striatum, and thalamus [7, 42]. The VMPFC, particularly the region known as the orbitofrontal cortex (OFC), is thought to evaluate choice options and encode outcome expectations [43]. The VMPFC projects to the LPFC, as do the insula cortex and ACC [7, 42]. The LPFC integrates the information received from these regions, as well as information received from the somatosensory cortex via the basal ganglia and is generally thought to be responsible for making decisions concerning what action to take [44]. More recent research [45] has suggested that this decision is made by the frontopolar cortex (FPC) and merely activated by the LPFC. However, this decision will be greatly affected by the individual’s level of motivation, the mechanisms of which depend on activation of the dopaminergic midbrain systems, the substantia nigra pars compacta (SNc) and ventral tegmental area (VTA), and the locus coeruleus (LC)-noradrenergic system [7, 41].

**3.1. Catecholamines and motivation during cognition and exercise**

 Before and during cognition, exercise or indeed any activity, projections from the DLPFC to the hypothalamus initiate activation of the dopaminergic midbrain systems [46]. Moreover, afferent information from lamina Ⅰ and NTS axons directly and indirectly activate cell groups A1,-A2, A5-A7 and C1. Activation of these cell groups can lead to increased noradrenaline release from the LC [47-49] and, indirectly, increased dopamine from the SNc and VTA [50-51]. The dopaminergic neurons in the PFC carry out a number of very important functions with regard to motivation. However motivation is also affected by dopaminergic neurons in the basal ganglia, particularly the dorsal striatum, which also receive input from the SNc and VTA. Dopaminergic neurons exhibit two types of firing, tonic and phasic. At low levels of stress, tonic discharge is slow and there is little or no phasic release of dopamine. During moderate levels of stress, such as during moderate intensity exercise and undertaking complex cognitive tasks, tonic firing is at a moderate level and phasic bursts are generally stimulated. During high levels of arousal or stress, tonic firing is fast with little or no phasic bursts, which has a negative effect on neural activity [46, 52].

 Dopaminergic neurons activated in the nucleus accumbens core are crucial for enabling motivation to overcome response costs, such as physical effort or sustained attention to a cognitive task; and for an enhancement of general motivation [46]. It has also been shown that during phasic bursts, dopamine neurons code the prediction errors, i.e. differences between predicted sensations and actual feelings [53]. Furthermore, there is evidence to show that dopaminergic neurons, which project to the VMPFC, nucleus accumbens shell and the dorsal striatum encode motivational value, while projections to the DLPFC and nucleus accumbens core evaluate motivational salience [46].

 The effects of motivation are also dependent on noradrenaline synthesis and release primarily from the LC, which receives direct or indirect input from the hypothalamus, ACC, VMPFC, amygdala and NTS. With regard to motivation, it is most likely that top-down projections from the ACC and VMPFC are important in initiating LC release of noradrenaline [54]. DLPFC will also have an indirect effect via the hypothalamus. As with dopamine, at low levels of stress release is tonic and slow with little or no phasic activation. As stress increases, so does the rate of tonic release. Phasic discharge, which is triggered by bottom-up input mechanisms involving novel/salient sensory stimuli and top-down decision making processes, occurs almost exclusively during moderate tonic release. This phasic activity appears to be necessary for maintenance of goal-related action [54]. Thus, as with dopaminergic neurons, noradrenergic neurons are affected in an inverted-U fashion with regard to goal maintenance. Moreover, research has shown that whereas dopaminergic neurons appear to encode the expected reward and anticipate the effort cost (perception of effort), noradrenergic neurons mobilize resources in order to energize the behavior necessary for successful completion of the task [54]. Aston-Jones and Cohen claim that the VMPFC and ACC, which project to the LC, initiate phasic bursts of noradrenaline activation when goal directed behavior is determined to be effective but induce tonic activity when the rewards are thought to be not worth the cost. So, as we saw above, phasic activity ensures a positive effect on goal maintenance but tonic activation of noradrenaline is believed to be facilitative of searching for alternative goals when rewards are thought not to be cost worthy [54].

**4. Conclusion**

 Examination of the reviews in section 1, shows that submaximal exercise is negatively affected by mental fatigue. Also, consistent with Brown et al. [6], shorter and longer cognitive tasks tend not to differ in their effect on subsequent exercise. This appears somewhat counterintuitive. Interoception during the exercise task requires the individual to compare the predictive sensory consequences, held in the AIC, with feedback from the spinothalamic and medullothalamic afferents to the AIC, in order to decide whether to stop, slow down or continue at the present pace [7, 39]. While it is natural to think that reproducing maximal performance is more difficult than reproducing submaximal performance, the reproduction of submaximal effort, or pacing, is not only demanding physically but also perceptually, as it involves a judgment regarding the pacing. Thus, the individual may predict the sensory consequences during submaximal exercise as being more demanding than in a maximal performance task, where the perceptual demands are less. If this is the case, the person is also likely to perceive themselves as having less resources available than in the control situation due to the perceived cognitive fatigue. Thus, affecting the decisions made by the interaction between the AIC, ACC and VMPFC.

 With regard to shorter cognitive tasks having a greater negative effect than longer ones, this is probably due to the fact that many of the cognitive tasks have large learning/habituation effects [55, 56]. If the task is undertaken for a short period of time, one in which learning has not taken place, the person is most likely to perceive it as requiring a lot of energy and the DLPFC corollary discharge to the AIC will probably predict greater negative feedback during the exercise test than in the control condition. When learning takes place, the task is more likely to be perceived as requiring less energy and the predicted sensory consequences will be less negative. This will have the same effect on perception of effort cost and availability of resources as with the shorter versus longer tasks outlined above, with the same effect on the AIC, ACC and VMPFC interactions..

 Theoretically, this process is affected by motivation [1-3, 6], yet the reviews showed no empirical data to support a role of motivation. Interestingly, Brown and Bray [57] demonstrated that a monetary reward attenuated the negative effect of mental fatigue on subsequent physical performance . The ACC and VMPFC, particularly the OFC, interact to evaluate the options available and encode outcome expectations [43]. In the AIC, ACC, striatum and VMPFC, dopaminergic neurons encode the expected reward and evaluate the effort cost, while noradrenergic neurons determine the available resources. A decision as to what to do is then made. If activation is to be continued, phasic catecholamines release is continued but if the decision is negative, the ACC and VMPFC initiate tonic release from the LC [54]. This results in slowing down or stopping, which requires activation of the FPC and LPFC [45]. Müller and Apps [58] see maintaining motivation as being effortful in itself and thus inducing perceptions of fatigue. They termed this “motivational fatigue” (p. 143). While psychobiological theories [59] of central fatigue see perception of insufficient resources as being the essence of central fatigue. Furthermore, theta band activity during cognition has been shown to affect subsequent physical activity [60] and is thought to be indicative of motivation and perception of effort cost [61]. Thus theoretically the role of motivation is well-supported. The failure of research to demonstrate an effect of motivation, may be because the tests are very subjective. Future research may consider utilizing pupillometry to measure changes in dopamine brain concentrations [62]. Moreover, interoceptive responses to motivation are also affected by psychological factors. Decisions concerning prediction of sensory consequences, reward evaluation and available resources are dependent on past experiences, short and long-term goals and perception of fitness level [39]. Further research can manipulate these factors to examine the effects of experience, as can training studies.

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**Conflicts of Interest**

Terry McMorris declares that he has no conflicts of interest relevant to the content of this article.

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**Figure legend.**

Figure 1. Schematic of afferent activation in the interoceptive system.

ACC anterior cingulate cortex: AIC anterior insula cortex: DLPFC dorsolateral prefrontal cortex: FPC frontopolar cortex: VLPFC ventrolateral prefrontal cortex: VMPFC ventromedial prefrontal cortex: S1 somatosensory cortex.