Central fatigue theory and endurance exercise: toward an interoceptive model

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Abstract

We propose a model of exercise-induced central fatigue based on interoception and motivation. Predictions of the expected sensory feedback are fed forward by the dorsolateral (DL) prefrontal cortex (PFC) to the anterior insula cortex (AIC). During exercise, the AIC receives feedback from lamina Ⅰ lateral spinothalamic and nucleus tractus solitarii medullothalamic pathways. The feedback is compared to the predictions in order to generate a current awareness state, which is forwarded to the anterior cingulate cortex (ACC), ventromedial (VM)PFC and lateral (L)PFC. The LPFC integrates the information and makes a decision as to whether to continue or stop. The decision is dependent upon interaction with the substantia nigra pars compacta and ventral tegmental area dopamine (DA), and locus coeruleus (LC)-norepinephrine (NE) systems. Phasic activation of DA and NE neurons appears to be necessary for maintenance of goal-related action but the VMPFC and ACC, which project to the LC, induce tonic NE activity when the rewards are thought to be not worth the cost thus fatigue is perceived.

Key words: 5-hydroxytryptamine: insula cortex: anterior cingulate cortex: dorsolateral prefrontal cortex: ventrolateral prefrontal cortex: ventromedial prefrontal cortex: substantia nigra pars compacta, ventral tegmental area: locus coeruleus, dopamine: norepinephrine: motivation

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1. Introduction

Fatigue is an encompassing term which includes impairments in the ability to perform physical tasks or to produce muscle force as well as sensations that relate to tasks being more difficult or taking more effort than expected (Taylor & Gandevia, 2008). Fatigue can originate from both ‘peripheral ‘and ‘central’ mechanisms. The nature of peripheral fatigue, i. e. force reductions occurring due to processes distal to the neuromuscular junction (Carroll et al., 2017), has received much attention (see Allen et al., 2008; Kent-Braun et al., 2012; Debold et al., 2016 for reviews) and is relatively well understood . However central fatigue, which has been defined as the inability of the brain to maintain the drive necessary to produce the desired force or power output (Davis & Bailey, 1996) and refers to processes within motoneurons and the central nervous system (Carroll et al., 2017), is perhaps less well-understood. In particular, and as noted previously (Taylor & Gandevia, 2008), the study of exercise-related ‘central’ fatigue has, historically, focused on the performance of the motor system, and less on the more cognitive aspects of fatigue. Yet, anecdotal evidence, often in the form of “ghosted autobiographies” of athletes, shows that the role of cognition or central fatigue during endurance exercise has been known to be very important for many years. Its relationship with peripheral fatigue is less clear.

In sub-section 1.1, we briefly describe the role of the brain in motor control, while in section 2 we outline and critique the major neurochemical theories of central fatigue. In section 3 we examine the major psychophysiological theories. These theories have been developing over a number of years although comparatively recent research into the neuroanatomy of feedback from peripheral afferents to the brainstem and higher centers of the brain (Craig, 1995; 2003; 2004a;

2004b) has led to some interesting developments with regard to the mechanisms thought to account for central fatigue (see Hilty et al. 2011; Robertson & Marino, 2016). In section 4, we elaborate on these mechanisms and suggest how the nature of Craig's (2002; 2015) interoception theory provides a viable explanation of the causes of central fatigue. To Craig, interoception is not merely a neuroanatomical phenomenon but is an emotional response which is heavily influenced by motivation. Therefore, we include in our model an account of the role of catecholamines in motivation, particularly with regard to maintaining goal directed behavior, but also how this is affected by exercise-induced alterations in brain catecholamines concentrations. The interaction between exercise and brain catecholamines concentrations does not only affect motivation but also the whole process of central fatigue, as dopamine (DA) and norepinephrine (NE) are vital for activation of the prefrontal cortex (PFC), which is thought to control central fatigue (Klass et al., 2016; Robertson & Marino, 2016).

1.1. Overview of the role of the brain in motor control

Insert Figure 1 about here

Figure 1 provides a schematic of the roles of the different regions of the brain during motor control. The decision to undertake physical exercise is thought to be initiated by the dorsolateral (DL)PFC and may come from internal or external input. The supplementary motor area (SMA) is mostly concerned with internal factors, while the premotor cortex (PMC) is more readily activated by external stimuli. The SMA and PMC make direct connections with the spinal cord via the cortico-spinal tract or indirectly via connections with the primary motor cortex (M1) and brainstem. The pre-motor and motor regions of the brain, and indeed most of the cerebral cortex, feedforward to the basal ganglia (BG) and cerebellum, forming the cerebral-BG-thalamo-cerebellar pathway. Moreover, regions projecting forward to the cerebellum, via this

pathway, receive ascending feedback from the cerebellum. These closed-loop connections between the BG and cerebellum play a major role in motor control (Doya, 2000; Shadmehr & Krakauer, 2008).

The feedforward to the cerebellum is in the form of corollary discharge. The somatosensory cortex also receives corollary discharge from M1 (Enoka & Stuart, 1992). Corollary discharge informs the cerebellum and somatosensory cortex of the expected sensory consequences of performing the movement correctly. When movements are performed very slowly, corollary discharge can be compared with the actual sensory feedback and changes to the action can be made. Afferent feedback to the somatosensory cortex is via the dorsal column-lemniscal pathway, which consists of large dynamiter sensory fibers from the skin, muscles and joints, and the ventral spinothalamic pathway, which originates in lamina Ⅴ and lamina ⅤⅠⅠ. In most cases, feedback arrives too late for the individual to use it to control on-going movement. The problem is overcome due to the plasticity of the cerebellum. Through experience, the cerebellum learns to anticipate errors and alter subsequent movements rather than try to alter the on-going movement. In other words, it develops internal templates that predict the sensory outcomes of motor commands and corrects motor commands through internal feedback. This results in smooth coordinated actions. Although this is probably the most common mechanism used by the cerebellum to control movement, it is generally agreed that when possible, mixed feedforward and feedback control is the best strategy, combining the efficiency of anticipatory action with feedback control (Herreros & Verschure, 2013).

The above briefly outlines the brain mechanisms involved in motor control in non-fatiguing actions. However, as we will see in the following sections, there is some disagreement between theorists as to the part played by corollary discharge and afferent feedback to the

104 somatosensory cortex, wjth regard to central fatigue. In the next two sections, we examine the
105 major central fatigue theories.
106
107 **2. Neurochemical theories of central fatigue**
108 *2.1. Serotonin hypothesis*
109 It has long been acknowledged that 'central' factors play a role in the development of
110 fatigue (see Gandevia, 2001 for seminal review) and that during sustained muscle contraction,
111 the maximal effort that can be achieved voluntarily is less than that which can be achieved when
112 the muscle is activated directly by electrical stimulation of the motor nerve (e.g. Asmussen,
113 1979) . These observations led the Oxford University biochemist, and marathon runner, Eric
114 Newsholme, to propose that the neuromodulator 5-hydroxytryptamine (5-HT), also known as
115 serotonin, might be a prime candidate for explaining central fatigue (Newsholme et al., 1987).
116 Given the mechanisms by which Newsholme et al. (1987) perceived 5-HT to act on the brain
117 during fatiguing exercise, they termed the theory, the tryptophan-5-HT-central fatigue theory. It
118 is now more commonly known as the serotonin theory.
119 Newsholme et al. (1987) were aware of the commonly held belief that 5-HT induces
120 lethargy and sleepiness. Moreover, they were also aware that the precursor of 5-HT, tryptophan,
121 more readily crosses the blood-brain barrier during exercise than at rest. Tryptophan is found in
122 plasma either bound to albumin or unbound. Unbound or free tryptophan readily crosses the
123 blood-brain barrier. During exercise, free fatty acids displace tryptophan from binding with
124 albumin, therefore there is an increase in free tryptophan. This crosses into the brain and forms
125 5-HT (Blomstrand, 2006; Hawkins et al., 2006). Some albumin-bound tryptophan also crosses
126 the blood-brain barrier probably due to a dissociation mechanism that takes place at the surface

of the brain capillary endothelium (Pardridge, 1998). However, Fernstrom and Fernstrom (2006) questioned the role of free fatty acids and unbinding of tryptophan from albumin as the cause for exercise-induced increases in 5-HT concentrations but did agree that exercise likely induces increased brain concentrations of 5-HT.

Having crossed the blood-brain barrier, tryptophan is hydroxylated to 5-hydroxytryptophan (5-HTP), under the influence of tryptophan hydroxylase. It is further broken down by aromatic amino acid decarboxylase (AADC) into 5-HT. This process takes place in the raphe nuclei. This is the only place that 5-HTP is thought to be found. 5-HT is stored in vesicles, mainly the parafollicular cells of the thyroid (Lefebvre et al., 2001). Tryptophan hydroxylase is the rate-limiting enzyme for 5-HT synthesis and is not fully saturated under normal conditions, therefore increases in brain concentrations of tryptophan will facilitate 5-HT synthesis. Newsholme et al. (1987) received contemporary support from rodent studies, which demonstrated significant increases in brain 5-HT concentrations and/or concentrations of the 5-HT metabolite 5-hydroxyindoleacetic acid (5-HIAA) following exercise (Blomstrand et al., 1989; Chauoloff et al., 1986; 1987). More recent rodent studies have shown similar results (Caperuto et al., 2009; Chen et al., 2008; Chennaoui et al., 2001; Gomez-Merino et al., 2001; Langfort et al., 2006; Meeusen et al., 1996; Meeusen et al., 2001; Meeusen & De Meirleir, 1995). Moreover, Blomstrand et al. (2005) examined the brain uptake of tryptophan during prolonged exercise (3 h at 200 ± 7 W, on a cycle ergometer) in humans by calculating the arterial-venous difference (*a*-*v* diff) multiplied by plasma flow. They found large increases in cerebral uptake. However, as reported in a short but succinct recent review (Meeusen & Roelands, 2017), results from studies with humans, in which diet was manipulated to attempt to alter brain concentrations of tryptophan, have failed to support the 5-HT hypothesis.

The methods used in these nutrition studies were tryptophan ingestion and the increase of dietary uptake of branched-chain amino acids (BCAA). Tryptophan ingestion should lead to increased brain tryptophan concentrations, as it crosses the blood-brain barrier. Theoretically, this should induce earlier onset of fatigue. Dietary uptake of BCAA results in a lowering of brain concentrations of tryptophan. BCAA and tryptophan utilize the same blood-brain barrier facilitative transporter L1 (Hawkins et al., 2006), therefore following increased BCAA intake, there is more competition for the free-tryptophan (i.e. unbound from albumin) to access L1 in order to cross the blood-brain barrier. As a result, there will be less 5-HT synthesized by the raphe nuclei. Hence the inhibitory effect of 5-HT should be attenuated. That the studies failed to support the serotonin hypothesis led Davis and Bailey (1996) to examine a possible interaction between 5-HT and DA as causes of central fatigue.

2.1.1. 5-hydroxytryptamine-dopamine interaction effects

Based on the positive roles of DA in arousal, motor control and motivation, Davis and Bailey (Bailey et al., 1993; Davis & Bailey, 1996; Davis et al., 2000) hypothesized that a low ratio of brain 5-HT to DA favors improved performance but a high ratio of 5- HT to DA would lead to a lowering of arousal, loss of motor coordination and motivation. This they claimed was what caused central fatigue (Davis et al., 2000). This was based on the findings of Bailey et al. (1993), who examined the effect of exercise to exhaustion on the turnover of 5-HT and DA in the midbrain, striatum, hypothalamus and hippocampus of rodents. The authors included the effect of the use of selected drugs, but here we report only results for the placebo trials as our interest is in central fatigue in normal rather than pharmaceutically engineered situations. Measures were taken from rodents sacrificed after one hour as well as those sacrificed following exhaustion. 5-HT and its metabolite 5-HIAA demonstrated significant increases from rest to one hour in all

four brain regions measured and further increases in midbrain and striatum following exhaustion. This was similar to the results of Blomstrand et al. (1989) and Chauoloff et al. (1986), using similar methods. Results for DA and its metabolite 3,4 dihydroxyphenylacetic acid (DOPAC) were more complex, however. DA was increased after one hour in the midbrain and striatum only. At exhaustion it had returned to resting levels in the midbrain but remained higher than at rest in the striatum, although this was significantly lower than concentrations after one hour. In the midbrain, DOPAC was significantly higher than at rest after both one hour and exhaustion. Concentrations following one hour and exhaustion did not differ significantly from one another. In the striatum, after one hour, DOPAC was significantly higher than at rest and following exhaustion, while concentrations at exhaustion were significantly greater than at rest. There were no significant differences in the hypothalamus and hippocampus.

In the Abstract to their article, the authors stated "Brain dopamine (DA) and 3,4-dihydroxyphenylacetic acid (DOPAC) were higher at 1 h of exercise ($P < 0.05$) but were similar to resting levels at fatigue" (Bailey et al., 1993, p. 3006) and it is the implications of this comment which have tended to be used as support for a monoamine hypothesis of central fatigue. As we saw in the previous paragraph, the data suggest that the situation was not that straightforward and there is evidence of increased turnover of DA in the midbrain and striatum at exhaustion. Furthermore, Heyes et al. (1985) provided contradictory evidence regarding DA turnover at exhaustion. These authors examined the effect of exercise to exhaustion on concentrations of DA, DOPAC and another metabolite of DA, 4-hydroxy 3-methoxyphenylacetic acid also known as homovanillic acid (HVA), as well as 5-HT and 5-HIAA in the striatum, brainstem, and hypothalamus of rodents. They found increased concentrations of DA, DOPAC and HVA in the striatum and brainstem of exhausted rats. There were no significant effects in the

hypothalamus. 5-HIAA concentrations were increased in striatum but 5-HT concentrations were unaffected in all three brain regions. Blomstrand et al. (1989) demonstrated increased DA and 5-HT in the brainstem and hypothalamus, and 5-HIAA in the hippocampus and striatum of mice, at exhaustion. More recently, Hu et al. (2015) have shown increased extracellular DA and 5-HT in the subthalamic nucleus of rats at exhaustion. Observation of the data supplied by Hasegawa et al. (2008) suggests that DA concentrations in the hypothalamus at exhaustion were similar to those at rest, although the authors did not statistically compare concentrations at rest to those at exhaustion, Moreover, pharmacological and electrophysiological research into the interactions between 5-HT and DA neurons in non-exercise conditions has produced somewhat contradictory results (see Barnes & Sharp, 1999; Fink & Göthert, 2007; Olijslagers et al., 2006, for reviews), which may explain the issues with the 5-HT-DA interaction during exercise (see below).

That there is not strong support for the Bailey et al. (1993) theory may be due to the effects of different 5-HT or serotonergic receptors on DA synthesis and release. 5-HT modulates DA release in the substantia nigra pars compacta (SNc) and ventral tegmental area (VTA), and in their projection areas, the striatum and, the nucleus accumbens (NAc) and PFC respectively (Fink & Göthert, 2007). The 5-HT_{1A}, 5-HT_{1B}, 5-HT_{2A} and 5-HT_{2C} serotonergic receptors, in particular, interact directly and/or indirectly with DA neurons (Olijslagers et al., 2006) in these brain regions. Pharmacological and electrophysical studies with rodents tend to show that the 5-HT_1 serotoninergic receptors have an indirect facilitative effect on DA synthesis and release in these areas (Barnes & Sharp, 1999; Fink & Göthert, 2007). 5-HT_1 receptors couple to G_i/G_o guanosine triphosphate (GTP)-binding proteins and inhibit activation of the second messenger cyclic adenosine monophosphate (cAMP), thus dampening the effects of neuronal activity. However, 5-HT_{1B} receptors are probably located on inhibitory γ-aminobutyric acid (GABA)

219 interneurons rather than on DA projection terminals (Barnes & Sharp, 1999), while 5-HT_{1A}
220 receptors are probably located at the presynaptic terminals of GABAergic neurons
221 (Katsurabayashi et al., 2003). Therefore, they negatively affect the release of the inhibitory
222 neurotransmitter GABA, resulting in an indirect facilitation of DA release. 5-HT_{1A} neurons in the
223 dorsal raphe nucleus open K^+ channels but do not appear to affect the inhibition of cAMP,
224 therefore they also have a direct facilitative effect on DA release (Clarke et al., 1996).
225 The situation with the 5-HT_2 family is less clear. These receptors couple to $G_{\alpha q}/G_{II}$ GTP-
226 binding proteins and activate phospholipase C, resulting in an excitatory effect on 5-HT (Barnes
227 & Sharp, 1999). However, they have been shown to have an inhibitory effect on DA release in
228 the medial (m)PFC. This is because of neurons that are located on inhibitory GABAergic
229 interneurons, which probably activate $GABA_B$ receptors thus inhibiting DA release (Santiago et
230 al., 1995). The same process does not occur in the striatum where 5-HT_{2A} neurons do not appear
231 to affect DA release. Why and how this occurs is unsure and a matter of some debate (see Fink &
232 Göthert, 2007). Despite the inhibitory effect of 5-HT_{2A} receptors on mPFC DA release, 5-HT_{2A}
233 receptors in the mPFC have been shown to facilitate DA release in the VTA (Bortolozzi et al.,
234 2005; Puig et al., 2003). This may be due to activation of 5-HT_{2A} neurons that are located on
235 excitatory, glutamergic pyrimidal projection neurons rather than on GABAergic receptors. These
236 neurons project to the VTA area (Bortolozzi et al., 2005). It appears that the effects of 5-HT_{2A}
237 neurons on DA release depend on the brain region involved and the localized positioning of the
238 neurons. The situation with regard to 5-HT_{2C} is far more clear. These receptors are localized on
239 GABAergic interneurons in the dorsal raphe nucleus, therefore inducing an indirect tonic
240 inhibitory control on the DA release in both the NAc and the striatum.

The contradictory empirical results outlined above and the pharmacological and electrophysiological literature concerning the interaction between 5-HT receptors and DA release question the assertion that central fatigue is the result of 5-HT inducing reductions in brain DA release and metabolism. Meeusen and colleagues (e.g., Meeusen et al., 2001; Meeusen & De Meirleir, 1995) decided that the interaction between exercise, 5-HT, DA and central fatigue was incomplete and effects of the neurotransmitter NE, also known as noradrenaline, required investigation.

2.1.2. 5-hydroxytryptamine-catecholamines effects

DA and NE are part of the catecholamines family of neurohormones, along with epinephrine (Epi: also known as adrenaline), and are known to interact with one another to control activity in many regions of the brain (Arnsten, 2009; Gioanni et al., 1998). As a result, Meeusen's group have undertaken a large amount of research using systematic reviews, research with rodents and more recently pharmacological studies with humans, in order to determine the possible roles of 5-HT, DA and NE in central fatigue. In this sub-section, we examine their work and begin with a summary of their reviews into the effects of acute exercise on brain concentrations of 5-HT, DA and NE in animals.

In a recent article, McMorris et al. (2016) summarized Meeusen and colleagues reviews of animal studies (Meeusen et al., 2001; Meeusen & De Meirleir, 1995) as demonstrating increased DA concentrations, particularly in the brainstem and hypothalamus, during and immediately following acute exercise. Moreover, recent research has supported these results by showing increased DA concentrations in the hypothalamus (Kitaoka et al., 2010) and hippocampus (Goekint et al., 2012). Perhaps more importantly, Meeusen and colleagues demonstrated increased concentrations of DOPAC and HVA, particularly in the brainstem and

hypothalamus. However, they found that the effect of acute exercise on whole brain concentrations of NE in animals has shown either a decrease or no significant effect. On the other hand, Kitaoka et al. (2010) demonstrated increased NE concentrations in the hypothalamus, but Goekint et al. (2012) found no significant effect on NE concentrations in the hippocampus. However, Meeusen's reviews showed that animal studies have demonstrated increases in brain concentrations of the NE metabolite 3-methoxy 4-hydroxyphenylglycol (MHPG) in most brain regions. One can conclude that acute exercise does induce increased turnover of DA and NE in the brain, but with some regional variations.

The studies reviewed, however, were in sub-maximal intensity exercise, while our interest is in the effects of exhaustion. We have seen evidence for increases of DA and its metabolites at exhaustion in some brain regions in the previous sub-section, so here we will examine research into concentrations of NE at exhaustion. Only five studies have examined this (Barchas & Freedman, 1963; Blomstrand et al., 1989; Cicardo et al., 1986; Hasegawa et al., 2008; Moore & Lariviere, 1964). Where drugs were used in these studies, we report only the results for the placebo groups. In two of the experiments (Barchas & Freedman, 1963; Cicardo et al., 1986), whole brain concentrations of NE were decreased in the heat (23º C) but not at a moderate temperature (15º C). Moore and Lariviere (1964) showed significant decreases of NE in the heat (23º C and 37º C), however they did not examine effects in moderate temperatures. Blomstrand et al. (1989) found increased concentrations of NE in the striatum of mice but not in the brainstem, hypothalamus and hippocampus. Although not statistically comparing rest to exhaustion, Hasegawa et al. (2008) showed that NE concentrations in the hypothalamus at exhaustion were similar to those at rest, in a moderate temperature (18º C). MHPG was not measured in any of the studies, so it is difficult to comment on turnover, although Cicardo et al.

believed that their results were due to increased turnover. Given the limited research outlined above, we need to examine the neurochemistry literature on the interaction between 5-HT and NE, before we can discuss the possibilities of exercise-induced increases in 5-HT brain concentrations resulting in depletion of brain NE.

The processes by which 5-HT affects NE release are very similar to those affecting DA release. 5-HT_{1A} receptors have been shown to stimulate NE release particularly in the hippocampus (Done & Sharp, 1994; Hajo´s-Korcsok & Sharp, 1996), frontal cortex (Hajo´s-Korcsok & Sharp, 1996), hypothalamus (Suzuki et al., 1995), and VTA (Chen & Reith, 1995). 5-HT_{1A} receptors are probably located at the presynaptic terminals of GABAergic neurons (Katsurabayashi et al., 2003). They are coupled to G_i/G_o GTP-binding proteins and inhibit activation of the second messenger cAMP, thus inhibiting GABA release. As GABA is an inhibitor, this has the net effect of increasing NE release. 5-HT_{2C} receptors have an indirect inhibitory effect on NE release particularly in the PFC and locus coeruleus (LC). They are probably localized on inhibitory GABAergic interneurons and so induce an indirect tonic inhibitory control on NE release (Gobert et al., 2000). The effect of 5-HT_{2A} receptors is somewhat questionable. Gobert et al. raised doubts about any effect at all, but Szabo and Blier (2001) demonstrated an inhibitory effect on NE release from the LC. This, they argued, occurred because although the 5-HT_{2A} receptors are excitatory, they are probably located on GABA terminals, originating from the prepositus hyperglossi nucleus. The excitatory effect of the 5-HT_{2A} neurons leads to an increase of the degree of activation of $GABA_A$ receptors and thus a decrease in NE neuron firing. However, a recent study of central and peripheral neuromuscular function found that $GABA_B$ receptors in the motor cortex were more directly linked with the etiology of incremental peripheral and central fatigue (Goodall et al., 2018). Specifically, an

extended cortical silent period was evident with increasing peripheral fatigue, which is associated with $GABA_B$ activation, whereas an extended short-interval intracortical inhibition ratio, a marker of $GABA_A$ activation, did not occur. Long-lasting K^+-dependent stimulation-induced inhibitory postsynaptic potentials specific to $GABA_B$ activation are thought to be accountable for this result by contrast to the characteristic short-lasting Cl^--dependent response of the $GABA_A$ pathway (McCormick, 1992). Goodall et al. claimed that their results and those of previous researchers strongly suggest that $GABA_B$ receptors require a higher GABA concentrations or longer exposure to GABA than do $GABA_A$ receptors for activation. As we saw in 2.1.1, $GABA_B$ receptors inhibit DA activation (Santiago et al., 1995). Thus both DA and NE can be indirectly inhibited by 5-HT_2 receptors. These data offer a plausible link between peripheral and central neuromuscular fatigue, and cognitive fatigue. Nevertheless, given the research outlined above, the situation with regard to exhaustion is far from clear. In order to attempt to clarify the situation, below we examine the results of pharmacological studies in humans.

2.1.3. Pharmacological studies in humans

Research examining the effects of DA and/or NE reuptake inhibitors or agonists, on time to exhaustion in rodents, shows somewhat equivocal results (Gerald, 1978; Hasegawa et al., 2008; Heyes et al., 19 85;, Kalinski et al., 2001). However, Roelands and Meeusen (2010) cast some doubt on the strength of evidence with humans in temperate conditions. Administration of 5-HT reuptake inhibitors to humans has generally demonstrated no significant effect (Meeusen et al., 2001, Parise et al., 2001; Piacentini et al., 2002; Strachan et al., 2004), while others have shown time to exhaustion to be shortened (Davis et al., 1993 Wilson & Maughan, 1992). Meeusen et al. (1997) demonstrated no significant effect of a 5-HT_{2C} antagonist on performance.

Moreover, DA reuptake inhibitors have tended to show no significant effect (Onus et al., 2016; Piacentini et al., 2004; Roelands et al., 2008b; Watson et al., 2005), although a significant increase in time to exhaustion was demonstrated in one study (Swart et al., 2009). Similarly, NE reuptake inhibitors have shown no significant effect in some studies (Onus et al, 2016; Piacentini et al., 2002; 2004; Watson et al., 2005) but significant negative effects have been demonstrated in others (Klass et al., 2012; 2016; Roelands et al., 2008a). Notably the doses used in studies in which a negative effect of NE reuptake was demonstrated were higher than in the other studies. Jacobs and Bell (2004) administered the α_1-adrenoceptor agonist modafinil and demonstrated a significant increase in time to exhaustion. Although this appears to contradict the findings reported above, it probably does not. Modafinil is thought also to inhibit GABA release in the cerebral cortex, which indirectly results in increased DA levels (Ferraro et al. 1996). We should note that the results, which we outline above, are all from studies undertaken in temperate conditions. Studies examining performance in the heat (30 º C) have provided different results.

DA and DA/NE reuptake inhibitors induced improved behavioral performance in two studies (Roelands et al., 2008b; Watson et al., 2005) but not in a third (Onus et al., 2016). However, in all three studies, thermoregulation was negatively affected by the DA/NE agonists without a negative effect on exercise performance. The authors argued that motivation would appear to have been significantly, positively affected by increased DA and NE uptake and therefore able to overcome the desire to stop exercising. This is a logical conclusion given the nature of the study designs. Interestingly, Onus et al. also presented evidence to show that in the cooler condition, the drugs acted peripherally to alter the twitch characteristics of skeletal muscle. The authors claimed that this latter factor could explain the lack of improvements shown for DA/NE agonists in the temperate conditions in their and other studies. Contrary to these

results, the NE reuptake inhibitor reboxetine induced a decrement in outcome performance in the heat (Roelands et al., 2008a). It is possible that high concentrations of NE in the ventromedial (VM) PFC and ACC resulted in tonic firing of LC-NE neurons, which reduces drive to continue the present activity and search for alternatives (Aston-Jones & Cohen, 2005: see 2.1.4 and 4.1.1 for discussion of the effects of tonic versus phasic firing of NE neurons).

2.1.4. Issues with monoamine hypotheses

Roelands and Meeusen (2016) stated that the serotonin theory alone can not explain central fatigue but probably plays a large part in it. There is some evidence from pharmacological studies and from the neurochemical literature concerning the interaction between 5-HT neurons and catecholamines release to support the notion that 5-HT, DA and NE do, in fact, interact with one another but the interactions depend on which 5-HT receptors are involved, the regions of the brain in which they are found and more importantly their specific location on GABAergic or glutamergic neurons. Thus, the interactions are complex and are also affected by DA and NE interactions with one another and interactions between catecholamines and the Hypothalamic-Pituitary-Adrenal (HPA) axis hormones. However, we begin our critique by commentating on some much more fundamental issues concerning the interaction between acute exercise and brain catecholamines concentrations.

The basic premise of serotonin theory is that exercise induces increased brain concentration of 5-HT and these inhibit the release of DA and NE in the brain (Meeusen et al., 2006). This is seen as being important because the catecholamines neurotransmitters are vital in the whole process of motor control from the decision to act, and the on-line control of that action through to and including the decision to stop (central fatigue itself). Inhibition of DA and NE during this process is seen as being negative and leading to early fatigue. As we have seen above,

379 the inhibitory effects of 5-HT on catecholamines release are probably not as great as originally
380 thought, which may explain why the serotonin theory is not the definitive answer to central
381 fatigue. However, two fundamental issues with regard to the roles of brain catecholamines
382 concentrations have been ignored in the development of this theory. Firstly, exercise per se
383 induces increased brain concentrations of catecholamines (see McMorris 2016); and secondly,
384 catecholamines tend to have an inverted-U effect on control of brain activity particularly in the
385 PFC (Arnsten, 2011; Cools & D'Esposito, 2011).

386 The idea that acute exercise induces increased brain catecholamines concentrations was
387 originally based on the argument that although catecholamines do not readily cross the blood-
388 brain barrier, if circulating concentrations were high, the blood-brain barrier would be
389 compromised (Cooper, 1973). This was supported by the research of Samorajaski and Marks
390 (1962), who found that in mice, high concentrations of catecholamines were able to cross the
391 blood-brain barrier in the median eminence at the base of the hypothalamus and in the anterior
392 pituitary gland. More recently, it has been shown that peripherally circulating Epi and NE
393 activate β-adrenoceptor chemoreceptors on the vagus nerve. The excitatory neurotransmitter
394 glutamate mediates synaptic communication between the vagal afferents and the nucleus tractus
395 solitarii (NTS), allowing noradrenergic cells in the NTS, which project to the LC, to stimulate
396 NE synthesis and release to other parts of the brain (Miyashita & Williams, 2006). It was thought
397 that this would occur following the lactate threshold (LT), which marks the beginning of an
398 exponential rise in peripheral blood lactate concentrations (Podolin et al., 1991) and hence
399 significant increases in circulating Epi and NE. Indeed, Soya and associates (Ohiwa et al., 2006;
400 Soya et al., 2007), experimenting with rodents, have shown that acute exercise above LT induces
401 c-Fos expression, which is indicative of neuronal activity, in what Dahlstroem and Fuxe (1964)

termed the A1 and A2 noradrenergic neurons in the NTS. Moreover, Ohiwa et al. also demonstrated that exercise below LT can induce similar changes. Activation of the NTS at sub-LT intensities is extremely unlikely to have been the result of circulating plasma catecholamines activating β-adrenoceptors on the vagus nerve. However, afferent signals from mechanoreceptors, or more accurately stretch receptors, in the heart and lungs, are fed back to the NTS via the vagus nerve (Berthoud & Neuhuber, 2000; Moor et al., 2005; Mravec, 2006). Similarly, arterial baroreceptors provide feedback, concerning blood pressure, to the NTS via the glossopharyngeal and vagus nerves (Kougias et al., 2010). Heart rate, tidal volume and blood pressure begin to increase immediately that exercise begins (Watson, 1974), and the feedback allows the hypothalamus to initiate activation of the sympathoadrenal system, culminating in the synthesis and release of catecholamines, in anticipation of increased exercise intensity (Mason et al., 1973; McMorris et al., 2009). Thus, it is not surprising to see c-Fos expression in A1 and A2 neurons in the NTS even prior to the LT.

Rodent studies have also shown that acute exercise induces c-Fos expression in adrenergic C1 neurons in the rostral ventrolateral medulla (Abbott et al., 2013; Barna et al., 2012). C1 neurons project to the LC (Abbott et al., 2012; Guyenet et al., 2013) and are the most likely to establish glutamergic synapses with the LC, although A1 and A2 neurons also innervate the LC (Holloway et al., 2013; Rinaman, 2011). C1, A1 and A2 neurons also have an indirect effect on the LC via projections to the hypothalamus (Guyenet et al., 2013; Rinaman, 2011), which in turn projects to the LC (Aston-Jones et al., 1986), the main source of NE in the brain.

A1, A2, A5 and A6 or LC neurons also project to the VTA (Mejías-Aponte et al., 2009), where they activate α_1-adrenoceptors. Grenhoff and associates (Grenhoff, & Svensson, 1993; Grenhoff et al., 1993) have shown that stimulation of the α_1-adrenoceptors by NE release from

the LC potentiates the firing of DA neurons in the VTA. This is probably due to α_1-adrenoceptor activation inducing enhanced glutamate release, which affects the excitability of DA neurons (Velásquez-Martinez et al., 2012). Also, these noradrenergic neurons, along with the adrenergic C1 neurons, project to the retrorubral field (RRF) in the reticular formation and stimulate DA activation there (Rinaman, 2011). The VTA and RRF have projections to the PFC.

Given the literature outlined above, it is not surprising to find rodent studies demonstrating exercise-induced increases in brain catecholamines and their metabolites (Meeusen & De Meirleir, 1995; Meeusen et al., 1997; 2001) and this will undoubtedly reduce the effects of 5-HT inhibition of DA and NE release in the brain. Research into serotonin theory has been based on the hypothesis that 5-HT inhibition of DA and NE release would have a negative effect on brain activity, however there is much evidence to show that the catecholamines neurotransmitters affect brain activity in an inverted-U manner (Arnsten, 2011; Clatworthy et al., 2009; Cools & D'Esposito, 2011), which may well mean that 5-HT inhibition of DA and NE concentrations may, in fact, be beneficial to the brain by helping maintain optimal levels of catecholamines. Below, we outline the mechanisms by which catecholamines and their receptors induce an inverted-U effect and return to how this might affect central fatigue in 4.1.1.

The roles of DA and NE, and their receptors have been extensively examined in the PFC and it is this region that provides the largest evidence for an inverted-U effect. The dopaminergic D_1-receptor is common in the PFC. D_1-receptors couple to G_s and G_{olf} GTP-binding proteins and stimulate cAMP activation, which amplifies the effects of neuronal activity. When DA concentrations are moderate, D_1-receptors dampen neural 'noise' by increasing GABAergic interneuron release which inhibits firing to non-preferred stimuli (Gorelova et al., 2002). Similarly, when NE concentrations are moderate, the high affinity α_{2A}-adrenoceptors are

activated. These are coupled to Gi/Go proteins and activation inhibits adenyl cyclase activity, and closes hyperpolarization-activated cyclic nucleotide-gated (HCN) channels, which increases the strength of neural signaling in the preferred direction, i.e. enhances the strength of the signal (Wang et al., 2007). Hence D_1-receptors and α_{2A}-adrenoceptors working together strengthen the signal to noise ratio. However, as catecholamines concentrations increase to levels thought to be found in an individual reaching exercise-induced fatigue, the position changes because during exercise high concentrations of NE are thought to activate the lower affinity α_1- and β-adrenoceptors in the PFC (McMorris, 2016). α_1-adrenoceptors are coupled to Gq/G_{11} proteins which activate phospholipase C, causing increased Ca^+ release and protein kinase A activity in the cell. This inhibits intracellular signaling. β-adrenoceptors are coupled with G_S proteins which increase cAMP activity resulting in the activation of protein kinase A and the dampening of neuronal activity. There is also increased activation of D_1-receptors which increases cAMP activation. Arnsten (2009; 2011) claimed that high levels of cAMP opens HCN channels throughout the dendrite, thus weakening network inputs from all directions. This would mean that the efficiency of the PFC is greatly diminished.

Moreover, DA and NE neurons both exhibit two different types of firing, tonic and phasic. In DA neurons, interaction between tonic and phasic discharge affects the PFC, and other brain regions, in an inverted-U manner. Phasic activation occurs during moderate tonic firing and is stimulated by salient stimuli. It is inhibited by faster tonic firing. (Bromberg-Martin et al., 2010). The situation is similar with NE neurons. Tonic rates largely fluctuate according to arousal levels and behavioral states. Phasic bursts are triggered by by bottom-up input mechanisms involving novel/salient sensory stimuli and top-down decision-making processes

(Devilbiss & Waterhouse, 2011). Phasic firing is most common during moderate tonic discharge and is inhibited by fast tonic discharge (see 4.1.1 for more detail).

The situation is exacerbated by the fact that heavy and long-duration, moderate intensity exercise stimulate the synthesis and release of the HPA hormone cortisol (corticosterone in animals). It is generally thought that exercise needs to be ≥ 80% maximum volume of oxygen uptake ($\dot{V}O_{2MAX}$) (De Vries et al., 2000; Hill et al., 2008; McMorris et al., 2009) or to be of at least 45 mins in duration (Bridge et al., 2003; Jacks et al., 2002; Shojaei et al., 2011) to affect plasma and salivary concentrations of cortisol. Cortisol and corticosterone readily cross the blood-brain barrier and rodent studies have shown evidence of acute exercise-induced increases in corticotropin releasing factor (CRF) mRNA expression in the paraventricular neurons (PVN) of the hypothalamus (Hand et al., 2002; Jiang et al., 2004: Kawashima et al., 2004; Timofeeva et al., 2003; Yanagita et al., 2007). Synthesis and release of CRF is the first stage in the synthesis of cortisol/corticosterone. CRF receptors are found on LC neurons (Van Bockstaele et al., 1996) and this results in increased NE release in the PFC (Höglund et al., 2000). Also, glucocorticoids block the transporters on glia that normally remove catecholamines from the extracellular space (Pruessner et al., 2004). Thus, increased HPA activity can increase NE synthesis and release.

Other regions of the brain also show an inverted-U effect of catecholamines activation. Research into the effect of DA on activation of neurons in the striatum demonstrated that pharmacological or iontophoretic administration of DA had a positive effect on human and non-human animals who had low levels of DA at baseline but had a negative effect on those with high levels at baseline (Clatworthy et al., 2009, Vytacil et al., 2014). Unlike with the PFC, where D_1-receptors are mostly involved, in the striatum the main effect is on D_2-receptors, which are coupled to Gi/Go GTP-binding proteins and inhibit adenyl cyclase activity. The nature of the

493 neural discharge, tonic or phasic also affects striatum efficiency particularly when concerning
494 motivation (Seamans & Yang, 2004)

495 An inverted-U effect was also shown in the ventroposterior medial thalamus and
496 somatosensory cortex (Devilbiss & Waterhouse, 2004; Devilbiss, Page & Waterhouse, 2006),
497 however the inverted-U effect is not always demonstrated in these regions. It is thought that in
498 these regions, facilitation of excitatory responses is mainly mediated by α_1-adrenoceptors, while
499 suppression of evoked-activity is likely a result of NE acting on postsynaptic α_2- or β-
500 adrenoceptors (Devilbiss & Waterhouse, 2011). However, CRF can induce tonic firing of LC-NE
501 neurons, which results in suppression of signal transmission within the somatosensory thalamus
502 and cortex (Devilbiss et al., 2012) and this appears to reduce detectability of low-intensity
503 stimuli without affecting high-intensity stimuli (Devilbiss & Waterhouse, 2002; Moore, 2004).
504 Arnsten (2011) claimed that this allowed for quick and accurate detection of stimuli which
505 indicate danger.

506 Although we believe that the failure to take into account the inverted-U effect of
507 catecholamines in the brain, the role of differing monoamine receptors and the tonic versus
508 phasic firing of DA and NE neurons is a weakness in the neurochemical theories, we must
509 acknowledge that evidence for heavy or long-duration, moderate intensity exercise having the
510 same effect on humans as the stress imposed on rodents, during heavy exhausting exercise, is
511 weak. The fact that several authors (Onus et al., 2016; Piacentini et al., 2004; Roelands et al.,
512 2008b; Watson et al., 2005) showed that in temperate conditions, DA reuptake inhibitors did not
513 affect performance and that NE reuptake inhibitors only had an effect when the dose was very
514 high (Roelands et al., 2008a), strongly suggests that maximal intensity exercise in humans does
515 not have the same effects on brain catecholamines as that shown in rodents. This is probably

because the rodents need to be forced to exercise at these intensities. Even in sub-maximal exercise with rodents, this has been shown to result in higher concentrations of brain CRF and corticosterone in forced exercise compared to voluntary exercise (Droste et al., 2008). Furthermore, research with animals has shown that in extreme stress, the PFC is taken off-line (Arnsten, 2011), probably due to D_1-receptors, α_1- and β-adrenoceptors dampening all neural activity in the PFC. If this occurred in humans, central fatigue would not be under PFC control. Moreover, research examining the effect of acute exercise on cognition, while showing optimal effects during moderate intensity exercise, supplies only limited support for a deterioration in central executive activity, which is dependent on PFC activation, and certainly does not show a complete shut-down as stress studies with rodents suggest (McMorris & Hale, 2012). This is important because the proponents of psychophysiological theories of central fatigue claim that the PFC is key to perception of effort and fatigue, and the decision to abort activity (Noakes et al., 2004; Marcora et al., 2009). This could only occur if catecholamines concentrations at exhaustion were at or just over the top of the inverted-U.

To summarize this critique, we can say that there is some support for an interaction between 5-HT, catecholamines and HPA hormones during exercise, and that this may be involved in central fatigue. However, alone it most definitely does not provide strong evidence of being the major influence. therefore in the next section, we examine the literature on the major psychophysiological or psychobiological theories of central fatigue.

3. Psychophysiological theories

3.1. 'Central governor' theory

In this sub-section, we examine a theory based in psychophysiology. Noakes and colleagues (Noakes, 2012; Noakes et al., 2004; St. Clair Gibson et al., 2006) have developed what has become known as the 'central governor' or 'central integrative' theory. Founded on the writings of the nineteenth century Italian physiologist, Angelo Mosso (see Di Giulio et al., 2006; Noakes, 2012) as well as the Nobel Prize winning physiologist A. V. Hill (Noakes & Marino, 2009), they claim that the organism attempts to maintain homeostasis, even during exercise, in order to self-protect. During exercise, there is great danger of homeostasis being violated. The physiological needs during exercise, if not checked, could damage the organism, therefore the brain terminates, or regulates, the activity before homeostasis is threatened (Noakes & Marino, 2009; Noakes, 2012). Indeed, there are empirical data consistent with this assertion. For instance, Kay et al. (2000) have shown that when participants were instructed to perform a 1 minute maximal sprint at 10 minute intervals during 60 minutes of self-paced cycling in a hot-humid environment, power output and the integrated electromyography signal were reduced in sprints 2-5, compared to sprint 1. However, during the final sprint, participants were able to return their power output and the associated integrated electromyography signal to near baseline (sprint 1) values. These data were interpreted as indicating that efferent drive was subconsciously controlled in a manner that maintained a 'muscle reserve' during sprints 2-5, which the participants were able to utilize during the final sprint as part of a regulatory process which served to prevent premature fatigue or physiological damage. Likewise, Amann et al. (2006) demonstrated that 5 km cycling time trial performance was impaired with hypoxia and improved with hyperoxia, relative to normoxia, yet peripheral (quadriceps) fatigue was not different between the conditions. This was interpreted as indicating that the locomotor muscle output is

560 determined to a significant extent by the regulation of central motor output to the working
561 muscle, in order that peripheral muscle fatigue does not exceed a critical threshold.

562 In examining how this might occur, Noakes and colleagues (Noakes, 2012; Noakes &
563 Marino, 2009; Noakes et al., 2004; St. Clair Gibson et al., 2006) have drawn heavily on Ulmer's
564 (1996) teleo-anticipation theory of psychophysiological feedback. According to Ulmer, efferent
565 signals feedforward to the spinal cord and muscles to initiate action. In turn, afferent signals
566 from the periphery feedback to a central 'black box' programmer or central governor, which
567 modifies the efferent commands. The programmer, however, does not simply compare the initial
568 efferent feedforward with the afferent feedback, but takes into account the expected end-point of
569 the exercise, past experience of similar activity, fitness level, nutritional status, arousal level and
570 many other aspects even motivation levels (Lambert et al., 2005). Thus the individual can teleo-
571 anticipate the necessary changes to be made to the efferent commands. Noakes and colleagues
572 make many references to the importance of knowledge of the end-point of the exercise or the
573 ability to predict the likely end-point (Lambert et al., 2005; Noakes, 2012; Noakes et al., 2004).
574 This appears to be very important for teleo-anticipation but it does not, however, explain why the
575 individual terminates exercise at any given point, this is thought to depend on the person's
576 perception of fatigue.

577 St. Clair Gibson et al. (2003) saw fatigue as being a conscious sensation (perception is
578 probably terminologically more accurate than the word "sensation") rather than a physiological
579 occurrence. As we saw in the previous paragraph, during exercise afferent feedback is
580 continuously available to the central governor, allowing for changes to be made to the efferent
581 command. St. Clair Gibson and Noakes (2004) argued that although this process takes place at a
582 sub-conscious level, "the subconscious brain informs the conscious brain of an increasing neural

583 effort" (p. 801) as the individual experiences difficulty in maintaining homeostasis at the given
584 intensity. The brain is thought to interpret this as an "increased sensation of fatigue" (p. 801).
585 The central governor uses this information and other feedback including motivation level, to
586 produce a "homoeostatically (*sic*) acceptable exercise intensity" (p. 797). The calculation is
587 guided by knowledge of the end-point of the exercise. If the end-point is not known, the person
588 must draw on past experience and afferent feedback to teleo-anticipate the required output.
589 Interestingly, St. Clair Gibson et al. (2003) draw on the theory of Damasio (1993) from which
590 Craig (2002) developed his interoception model. More pertinently, Rauch et al. (2005) drew on
591 the neuroanatomy aspects of Craig's (2002) interoception theory to propose a mechanism
592 involving feedback from type Ⅲ and Ⅳ afferents to the insula cortex via the lamina Ⅰ
593 spinothalamocortical pathway. Furthermore, they claimed that projections from the insula to the
594 PFC may be used to determine whether to continue at the current pace or to make alterations.
595 Others (Hilty et al., 2011a; 2011b; Robertson & Marino, 2016) also supported the notion of
596 feedback from lamina Ⅰ afferents via the spinothalamocortical pathway to the insula as being a
597 potential source of information concerning perception of effort and fatigue (see section 4 for
598 more detail).

599 *3.2. Marcora's psychobiological theory*

600 Disagreement with the claims concerning the role of afferent feedback, posited by
601 proponents of the central governor/integrative theory, led Marcora et al. (2009) to propose an
602 alternative theory which they called psychobiological theory. However, as we will see in this
603 sub-section, there are many similarities between the theories, a point accepted by Pageaux et al.
604 (2014). According to psychobiological theory, there are five key factors involved in central
605 fatigue: "*1*) Perception of effort; *2*) Potential motivation; *3*) Knowledge of the distance to cover;

606 *4*) Knowledge of the distance covered/remaining; *5*) Previous experience/memory of perceived
607 exertion during exercise of varying intensity and duration" (Marcora, 2010, pp. 454-455). While
608 perception of effort is seen as vital by both groups, Marcora's notion of this factor is very
609 different to that of Noakes (2012). Marcora et al. (2009) saw perception of effort as depending
610 not on feedback but rather on corollary discharge, the expected sensory consequences of
611 performing the movement correctly, which is fed forward to the sensory regions of the brain. As
612 the individual tires or for some reason the task becomes more difficult, e.g. running uphill,
613 efferent commands need to be altered in order to meet the demands of the task. The increased
614 effort is consciously detected by the individual but any decisions, as to what to do, are dependent
615 on the other four factors.

616 Marcora (2010) used the term "potential motivation", rather than simply motivation, as it
617 refers to the amount of effort that the individual is willing to exert in order to be successful in the
618 task. Not surprisingly, it depends on a whole range of factors that determine motive strength at
619 any given point in time. Potential motivation will interact with knowledge of the distance to
620 cover, knowledge of the distance covered/remaining and previous experience/memory of
621 perceived exertion during exercise of varying intensities and durations, in order to decide
622 whether to attempt to continue with the activity or to terminate it. However, it is thought that at
623 this stage, there is conflict between competing responses, i.e. to stop or continue exercising
624 (Pageaux et al. 2014). Several authors (Marcora, 2009 Pageaux et al., 2014; 2015) have argued
625 that this requires activation of the pre-SMA and ACC, and these brain areas have been shown to
626 be activated during exercise.

627 *3.3. Summary of the similarities and differences between the psychophysiological theories*

Both theories are in agreement that corollary discharge plays a major role in controlling activity and that it is responsible for setting the initial parameters with regard to expected sensory consequences. To the proponents of the central governor theory (Noakes, 2012; Noakes et al., 2004), afferent feedback provides the brain with the necessary information to be aware when the task is getting difficult. To Marcora (2009), perception of effort is the "conscious awareness of the central motor commands to the locomotor and respiratory muscles" (p. 2061). Marcora does not deny that afferent feedback plays roles in a variety of physiological and perceptual responses, but denies that it has a role in perception of effort. However, there is a great deal of agreement concerning the factors taken into account to determine whether to continue or to terminate activity. Both groups agree that motivation is a key issue and that factors such as distance to be covered and past experience of similar activities are also important in decision making. There is also agreement that when the decision stage is reached, there is conflict between the "stop" and the "continue" responses. There is also some agreement on which brain regions are involved in this decision.

Proponents of the central governor theory have cited the insula cortex (Hilty et al., 2011a; Noakes, 2012; Williamson et al., 1999), the ventromedial (VM)PFC including the medial orbitofrontal cortex, the lateral (L)PFC, ACC, PMC, SMA and cerebellum (Hilty et al., 2011a; Mehta et al., 2009; Noakes, 20 12; Robertson & Marino; St. Clair Gibson et al., 2003) as interacting with one another to provide information to the central governor to decide whether to continue or stop. Whether it is this interaction that constitutes the central governor or one of these regions acts as the central governor is yet to be decided. Similarly, supporters of Marcora's psychobiological theory cite the ACC (Marcora, 2009; Marcora et al., 2009; Pageaux et al., 2014; 2015) and insula cortex (Marcora, 2009) but also the pre-SMA (Marcora, 2009 Pageaux et

al., 2014; 2015) as key to determine whether to continue or abort the exercise. The main concerns with brain regions in this theory appear to be the roles of these regions in response conflict.

4. Toward an interoceptive model of central fatigue.

In sections 2 and 3, we have outlined and critiqued the major neurochemical and psychobiological theories of central fatigue. While we acknowledge that these theories have played a major part in our understanding of this phenomenon, we believe that there are weaknesses that need to be addressed. The neurochemical theories have failed to take into account the differing properties of neuroreceptors and the roles of tonic versus phasic release of DA from the SNc and VTA, and NE from the LC. The inverted-U effect of catecholamines concentrations in the brain have also been ignored but, in fact, may not be as much of a problem as one might think (this is discussed in 4.1.1). The psychobiological theories highlight the role of corollary discharge from M1 but disagree regarding the roles of feedback to the somatosensory cortex. Nevertheless, they agree on the importance of perception of effort and also motivation. Given these issues, we propose a more holistic model based on Craig's (2000) interoception theory, which is dependent on feedback from the whole body concerning homeostasis, muscular activity, emotion and motivation. Moreover, we emphasize the interaction between exercise-induced increases and motivational increases in DA and NE, and the brain regions involved in decision making with regard to central fatigue.

4.1. Interoception and central fatigue

Sherrington (1948) saw interoception as being the perception of the physiological condition of the viscera but more recently it has been re-defined as the perception of "the

674 physiological condition of the entire body" (Craig, 2002, p. 655). These feelings have not only a
675 sensory, but also an affective, motivational aspect (Bubic et al., 2010; Craig, 2002). The
676 motivation to undertake exercise is thought to be controlled largely by the DLPFC (Spielberg et
677 al. 2012) but with input from other frontal regions, particularly the VMPFC (Szatkowska et al.,
678 2008) and ACC (Kounheir et al., 2009). We should, however, remember that the default
679 mechanism in humans is to maintain homeostasis, which may result in aborting an action sooner
680 rather than later. The DLPFC also controls initial top down strategies for achieving the goal
681 (Spielberg et al., 2012) and feeds forward a prediction of the expected sensory feedback to the
682 insula cortex (Craig, 2002). During exercise, we believe that the predicted interoceptive feedback
683 will depend on past experience of similar physical activity, the individual's perception of their
684 current fitness level, the subjective interpretations of the importance of the activity and whether
685 or not the person believes that their actions will be assessed or evaluated by significant others.
686 Directly competing against others is also most likely to affect the interoceptive predictions. One
687 would expect that the predictions will differ in competitive situations. Also, in training when the
688 individual is attempting to improve performance levels, predictions will have to change if the
689 individual is to move forward. Furthermore, the predictions will be influenced by the
690 individual's long-term goals, personality, and physical and social development (see Figure 2).
691 *Insert Figure 2 about here*
692 Based on interoception theory, the individual will make prediction errors even when they
693 have a large amount of experience of the task. As with corollary discharge in the cortico-BG-
694 thalamo-cerebellum pathway, the situation can not be predicted perfectly, therefore there has to
695 be continuous processing of afferent feedback (Craig, 2002). However, the interoceptive
696 feedback pathway (see Figure 3) is very different to the somatosensory pathway although it does

receive input from the somatosensory system. The situation when the person has no or very limited previous experience of the same or similar tasks, as in increasing distance or time during training, raises an issue for making predictions. The prediction errors would be great in initial trials at a new distance or speed but Paterson and Marino (2004) showed that the individual can comparatively quickly establish an "exertion template", which is altered "on-line" in subsequent trials and over time refined by the person.

Insert Figure 3 about here

The interoceptive feedback pathway begins in the spinal cord. During exercise, the lamina 1 lateral spinothalamocortical pathway is activated. Small-diameter Aδ- and C-type primary afferent fibers, which sense the physiological condition of all tissues of the body and terminate in lamina I of the spinal and trigeminal dorsal horns, relay afferent information in the lateral spinothalamic tract to the main homeostatic integration sites in the brainstem. The latter include regions that also receive vagal and glossopharyngeal afferent feedback via the NTS. The feedback includes information concerning a wide variety of physiological conditions, e. g. temperature, mechanical stress, blood pressure, acidic pH, hypoxia, hypercapnia, hypoglycemia and osmolarity (Craig, 2002, 2015). 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 (VMpo and VMb respectively) often described as the VMpo + VMb. The VMpo + VMb projects to the insula cortex but before discussing the very important implications of this projection, we should point out two important factors that we have not yet mentioned. Many of the brainstem cites that receive lamina Ⅰ and NTS inputs provide descending control of the autonomic nervous system and are heavily involved in control of homeostasis. Indeed, Craig (2015) claims that lamina Ⅰ and NTS connections indicate that their primary function is to

provide sensory input to the autonomic, preautonomic and homeostatic cell groups of the spinal cord and brainstem in order to maintain the health of the body. As part of this process, lamina I and NTS axons terminate on regions of the brainstem which contain concentrations of adrenergic and noradrenergic cells, particularly A1-A2 and A5-A7. As we saw in sub-section 2.1.4, activation of these cells can lead to increased NE release from the LC (Holloway et al., 2013; Rinaman, 2011) but also indirectly increased DA release from the SNc and VTA (Grenhoff, & Svensson, 1993; Grenhoff et al., 1993). We also know that exercise increases activity of these cell groups (Ohiwa et al., 2006; Soya et al., 2007).

Returning to the VMpo +VMb projection to the insula cortex, the afferent information is mapped firstly in the contralateral anterior insula cortex (AIC) and then, by way of a callosal pathway, a lateralized, second-order re-representation is made on the right AIC. This becomes consciously accessible, allowing the individual to make a subjective, affective perception of their physiological and emotional state. The AIC also receives afferent input from the somatosensory cortex (Gu et al. 2013). The AIC compares the interoceptive feedback with the top-down predictions of interoceptive state, which it received from the DLPFC, in order to generate a current awareness state (Gu et al., 2013). This is forwarded to the ACC, VMPFC and LPFC (Craig, 2002).

It is generally thought that the AIC and ACC work in conjunction with one another (Craig, 2002; Medford & Critchley, 2010). Craig described the insula as being a limbic-sensory cortex, because of its association with visceral sensation, and the ACC as a limbic-motor cortex, because of its association with autonomic and emotional control (Devinsky et al., 1995; Mesulam & Mufson, 1982). Similarly, Medford and Critchley (2010) stated that the AIC is responsible for the input and the ACC for the output components of interoception. This

743 interoceptive state is generated by the integrative functions of the AIC and then re-represented in
744 the ACC as a basis for the selection of and preparation for responses to inner or outer events
745 (Craig, 2002; 2015). The ACC is also part of the motivation/reward pathway and contains
746 neurons which are activated by positive motivation (Chudasama et al., 2013).We should note,
747 however, that ACC activation is also linked to aversive processing (Vogt, 2005; Johansen &
748 Fields, 2004).

749 The insula cortex and ACC have bidirectional projections with the VMPFC, which also
750 has connections with amygdala, striatum, and thalamus (Craig, 2002; Holroyd & Coles, 2002;
751 Singer et al., 2009; Williams & Goldman-Rakic, 1998). It is mainly involved in decision making
752 and motivation. It is seen as playing an important part in the maintenance of goal-directed
753 behavior. The VMPFC, particularly the region known as the orbitofrontal cortex which consists
754 of Brodmann's areas 10, 11 and 47 (Kringelbach, 2005), is thought to evaluate choice options
755 and encode outcome expectations (Schoenbaum et al., 2009).The VMPFC projects to the LPFC,
756 as do the insula cortex and ACC (Singer et al., 2009). The LPFC integrates the information
757 received from these regions, as well as information received from the somatosensory cortex via
758 the motor-somatosensory control system (see Figure 1), and is generally thought to be
759 responsible for making decisions concerning what action to take (Cole et al., 2013; Nee &
760 D'Esposito, 2016). These decisions are based on past experience and the motivational state of the
761 individual. Thus the LPFC has responsibility for continuing the action or stopping it. The LPFC
762 is well connected to the pre-SMA, SMA and PMC, which in turn inform M1 of the chosen
763 response. There is some disagreement as to the exact roles of the DLPFC and ventrolateral
764 (VL)PFC. Fehr and colleagues (Figner et al., 2010; Knoch & Fehr, 2007) claimed that the
765 DLPFC implements inhibition, while Aron et al. (2014) argued that the DLPFC determines task

rules or parameters, which we believe could set the level of interoceptive feedback that will indicate the need to stop. In line with Aron et al., we believe that it is the right VLPFC via projections to the pre-SMA, SMA and PMC that initiates the motor action of stopping. Writing specifically about central fatigue, Robertson and Marino (2016) took the sensible option and stated that it is the LPFC which controls the decision. Nee and D'Esposito (2016) provide evidence to show that when actions are aborted, the hierarchical control in the PFC is led by Brodmann's areas 45 and 46. Area 45 is in the VLPFC, while 46 is in the DLPFC, hence the use of the encompassing term LPFC is very appropriate. However, the efficiency of this interoceptive system is dependent on its interaction with the dopaminergic midbrain systems, the SNc and VTA, and the LC-NE system, particularly with regard to motivation.

4.1.1. Catecholamines

Before and during exercise, feedforward from the DLPFC to the hypothalamus initiates activation of the dopaminergic midbrain systems (Ballard et al., 2011; Bjorklund & Dunnett, 2007; Bromberg-Martin et al., 2010), although other brain regions receiving feedforward from the DLPFC, such as the mPFC, also project to the VTA (Adell & Artigas, 2004). The connections are bidirectional; and the ventromedial SNc and VTA project to the VMPFC, DLPFC and ACC (Holroyd & Coles, 2002; Williams & Goldman-Rakic, 1998). The DA neurons in these PFC regions carry out a number of very important functions with regard to motivation and interoception. However motivation is also affected by DA neurons in the BG, which also receive input from the SNc and VTA, particularly the dorsal striatum (Haber et al., 2000) including the NAc (Assadi et al., 2009). DA neurons activated in the NAc core are crucial for enabling motivation to overcome response costs such as physical effort; and for an enhancement of general motivation (Cardinal, 2006; Ghods-Sharifi & Floresco, 2010).

However, the actions of DA in these regions and its interaction with NE and 5-HT neurons mean that the effects are not straightforward. We have already seen in 2.1.2 that D_1-like and D_2-like dopaminergic neurons are affected differently by activation due to different effects on the second messenger and/or the location of the receptor with regard to GABAergic and glutamergic neurons. However, Bromberg-Martin et al. (2010) have shown that the nature of firing of the neurons also influences their effects. In a comprehensive review, they presented evidence for DA neurons exhibiting two different types of firing, tonic and phasic. Tonic discharge is controlled by a pacemaker conductance, which is a spontaneous, slow depolarizing membrane current that maintains the basal activity state of the neurons (Grace & Bunney, 1983). Phasic discharge, bursts of rapid firing of neurons, occurs in response to salient stimuli but the amplitude of the response depends on the level of tonic activity (Belujon & Grace, 2015). The more neurons that are firing during tonic discharge, the greater the phasic bursts, although not always as increases in extracellular DA during tonic discharge can attenuate the phasic burst firing-driven transient release (Floresco et al., 2003). This is likely to occur during high levels of stress (Arnsten, 2011) and is related to the inverted-U effect. At low levels of stress, firing is slow and tonic, which maintains the baseline level in downstream neural structures in order to ensure normal functioning of the neural circuits. During moderate levels of stress, tonic firing is at a moderate level and phasic bursts rapidly increase or decrease firing of DA neurons for 100-500 ms. This causes large changes in DA concentrations downstream and these last for seconds (Schultz, 1998; 2007). These phasic activations are triggered by reward prediction error. Waelti et al. (2001) showed that during phasic bursts, DA neurons coded the prediction error, which induced greater behavioral and neuronal learning than when predictions were as expected. This may well account for training effects where one would expect greater prediction error as the

person moves into unchartered territory. 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. Bromberg-Martin et al. (2010) also present evidence to show that one type of DA neurons encode motivational value. These are excited by prediction of reward but inhibited by aversive events. A second type of DA neurons encode motivational salience and are excited by both rewarding and aversive events. According to Bromberg-Martin et al. (2010), motivational value coding neurons project to the VMPFC, NAc shell and the dorsal striatum. Salience coding neurons are claimed to project to the DLPFC and NAc core.

The effects of motivation are also dependent on NE 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 NE (Aston-Jones & Cohen, 2005). DLPFC will also have an indirect effect via the hypothalamus. As with DA activity, the different families of adrenoceptors affect activity differently due to effects on the second messenger and also the type of neural firing, tonic or phasic. Tonic discharge is across a range of relatively slow rates (0.1–5.0 Hz), which is stochastically determined. Tonic rates largely fluctuate according to arousal levels and behavioral states. Basically it follows a linear pattern. Phasic discharge consists of brief 10–20 Hz bursts of two to three action potentials that is often, but not always, followed by a sustained suppression of spontaneous activity (200–500 ms) (Akaike, 1982). These bursts are triggered by bottom-up input mechanisms involving novel/salient sensory stimuli and top-down decision-making processes (Devilbiss & Waterhouse, 2011). Phasic activity appears to be necessary for maintenance of goal-related action and occurs during moderate tonic activity (Aston-Jones et al., 1999). Thus as with DA neurons, NE neurons are affected in an inverted-U

fashion with regard to goal maintenance (but see below). Moreover, research has shown that whereas dopaminergic neurons appear to encode the expected reward and anticipate the effort cost, noradrenergic neurons mobilize resources in order to energize the behavior necessary for successful completion of the task (Bouret et al., 2012; Varazzani et al., 2015). Aston-Jones and Cohen (2005) claim that the VMPFC and ACC, which project to the LC, initiate phasic bursts of NE 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 an inverted-U effect on goal maintenance but tonic activation of NE is believed to be facilitative of searching for alternative goals (Aston-Jones & Cohen, 2005; Usher et al., 1999) when rewards are thought not to be cost worthy. With regard to exercise, we would expect that when this point is reached, the VMPFC and ACC would feedback to the LPFC, which would abort the exercise.

With regard to the inverted-U effect, the changes in tonic and phasic firing that Aston-Jones and Cohen (2005) discuss are taking place in non-exercise situations. As we saw in 2.1.4, during exercise, feedback from the glossopharyngeal- and vagal-NTS pathways results in increased release of DA and NE in the PFC (Miyashita & Williams, 2006), thus there would be increased extracellular DA, which has a negative effect on DA phasic firing, while high levels of NE would induce tonic firing of NE neurons in the PFC. Such action would lead to a breakdown in the efficiency of the PFC which would mean that it would not be able to control central fatigue. The research of Roelands and colleagues (Onus et al., 2016; Piacentini et al., 2004; Roelands et al., 2008b; Watson et al., 2005), who showed that DA reuptake inhibitors did not negatively affect central aspects of fatigue and NE reuptake inhibitors did so only when doses were very high (Klass et al., 2012; 2016; Onus et al, 2016; Piacentini et al., 2002; 2004;

Roelands et al., 2008a; Watson et al., 2005), strongly suggests that maximal intensity exercise is not the same as high levels of stress. It would appear that at exhaustion, the concentrations of DA and NE are probably beginning to rise, which would increase tonic release at the expense of phasic firing of neurons. This would lead to the LPFC searching for alternatives to continuing the exercise, probably leading to central fatigue.

4.1.2. Summary

To summarize: our hypothesis differs from previous theories in that it proposes a holistic model which is based on corollary discharge to the insula cortex and feedback from the whole body not just the exercising musculature. It also integrates the roles of brain catecholamines in decision making concerning if and when to stop exercising. Furthermore, it involves the roles of DA and NE in motivation but adds the importance of tonic versus phasic release of DA and NE neurons, and how this impinges on the decisions to continue or stop exercising.

5. Implications for chronic fatigue

Several authors have suggested that chronic fatigue, as in chronic fatigue syndrome (CFS) or multiple sclerosis (MS) or Parkinson's disease (PD) or similar diseases, is a form of central fatigue (e.g. Dobryakova et al., 2015: Fukuda et al., 1994). Dobryakova et al. (2015), in what they termed the dopamine imbalance hypothesis, claimed that chronic fatigue was experienced because communication between the striatum and PFC was inhibited due to disruptions in DA signaling between these regions. Unlike with acute central fatigue, they point to low level concentrations of DA as being responsible for chronic fatigue. However, they also highlight the inverted-U effect and suggest that high pharmacologically-induced concentrations of DA may have a negative effect. Although they state that at present, there is no conclusive

evidence for high levels of DA to induce feelings of fatigue in individuals with CFS, MS, PD or any other similar disease.

The research of Salamone and colleagues (e .g; Salamone et al., 2003; 2012) examining the effect of DA on motivation to pursue effort-related choice behavior suggests a possible role for low levels of DA having a negative effect and possibly inducing feelings of fatigue, particularly chronic fatigue. They showed that DA in the NAc is inhibited by high concentrations of adenosine. In striatopallidal neurons, adenosine A2A receptors are co-expressed with dopamine D_2 receptors. When adenosine concentrations are increased, D_2 activation is decreased. Moreover, striatal adenosine A1 receptors have been shown to have an antagonistic effect on dopamine D_1 receptors (Shen & Chen, 2009). This occurs due to receptor-receptor crosstalk and interactions at the intercellular second messenger systems (Canals et al., 2003; Morelli & Pinna, 2001). As a result they claimed that motivation to carry out effort-related activity would decease. Chronic fatigue is thought to induce high levels of striatal adenosine (Dantzer et al., 2014). Indeed, caffeine-induced increases in the brain adenosine:DA ratio have been shown to negatively affect physical-endurance performance (Davis et al., 2003) and Pageaux et al. (2014) have argued that it could be a cause of central fatigue.

The interoception model itself could provide an explanation for chronic fatigue. As we have seen above, the insula cortex and ACC receive a wide range of physiological fedback via the lamina 1 lateral spinothalamocortical and NTS medullothalamic pathways. The insula cortex and the ACC are also connected to the amygdala, which store memories of aversive stimuli. This information is forwarded to the VMPFC which also has connections to the amygdala. As we saw above, the VMPFC is thought to evaluate choice options and encode outcome expectations (Schoenbaum et al., 2009). This suggest that aversive memories associated with CFS and other

diseases, which are held in the amygdala, will lead to the decision to avoid activity. This will particularly be the case when DA concentrations are low as in CFS, MS, PD and similar diseases (Dobryakova et al., 2015).

6. Conclusion

During exercise it would appear that what we have termed the motor-somatosensory control system, consisting of the cerebral-BG-thalamo-cerebellum pathway controls the actual movements but we believe that the key issue to central fatigue is the interoception control system. The DLPFC feeds predictions of the expected interoceptive feedback, in the form of corollary discharge, to the AIC before the exercise begins. These predictions are based on a variety of inputs, most important of which is probably past experience, however the predictions are heavily affected by emotion and motivation. In training situations or in competition, when the individual expects to have to exercise a higher intensity than they have previously experienced, the prediction is less easy to make than when they intend to reproduce a previous speed or intensity. However, even in these latter situations, the person has to continuously monitor the interoceptive feedback and make decisions concerning whether to continue, slow down, go faster or harder, or to stop. These decisions are heavily determined by the level of motivation and this motivation is under the control of the SNc- and VTA-DA, and LC-NE systems.

Although very high levels of stress lead to over-activation of D_1-like receptors, α_1- and β-adrenoceptors in the PFC, dampening all neural activity in the PFC and thus, in fact, taking the PFC off-line (Arnsten, 2011), this does not appear to happen in humans when exercise is the stressor. However, when the individual reaches exhaustion it may be that the catecholamines concentrations in the PFC are such that discharge moves from phasic firing to tonic. This has

been shown to lower the desire to maintain the goal-directed activity and induce the search for alternatives (Aston-Jones & Cohen, 2005), such as to stop exercising. On the other hand, it may simply be that during heavy exercise, the interoceptive feedback is at such a level that the person decides that they can not continue any further, or rather that continuing is not worth the cost required. If the individual thinks that further activity may injure them, they will stop. In other words, the levels of brain catecholamines concentrations at maximal intensity exercise may be such that the individual can still make an informed choice. They are probably not over the top of the inverted-U or certainly not far over the top, so the PFC is still working optimally or just-sub-optimally.

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Figure legends

Figure 1. Schematic of the roles of the different regions of the brain during motor control. DLPFC dorsolateral prefrontal cortex: SMA supplementary motor area: PMC pre-motor cortex: M1 primary motor cortex: BG basal ganglia: S1 somatosensory cortex.

Figure 2. Factors affecting interoceptive predictions.

Figure 3. Schematic of interoceptive feedback pathway. DLPFC dorsolateral prefrontal cortex: VLPFC ventrolateral prefrontal cortex: SMA supplementary motor area: PMC pre-motor cortex: M1 primary motor cortex: VMPFC ventromedial prefrontal cortex: S1 somatosensory cortex: VMpo posterior ventral medial nucleus of the thalamus: VMb basal ventral medial nucleus of the thalamus.

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