Developing the catecholamines hypothesis for the acute exercise-cognition interaction in humans: lessons from animal studies

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Abstract

The catecholamines hypothesis for the acute exercise-cognition interaction in humans fails to adequately explain the interaction between peripherally circulating catecholamines and brain concentrations; how different exercise intensities x durations affect different cognitive tasks; and how brain catecholamines, glucocorticoids, BDNF and 5-hydroxytryptamine interact. A review of the animal literature was able to clarify many of the issues. Rodent studies showed that facilitation of cognition during short to moderate duration (SMD), moderate exercise could be accounted for by activation of the locus coeruleus via feedback from stretch reflexes, baroreceptors and, post-catecholamines threshold, β-adrenoceptors on the vagus nerve. SMD, moderate exercise facilitates all types of task by stimulation of the reticular system by norepinephrine (NE) but central executive tasks are further facilitated by activation of α_{2A}-adrenoceptors and D_1-dopaminergic receptors in the prefrontal cortex, which increases the signal to 'noise' ratio. During long-duration, moderate exercise and heavy exercise, brain concentrations of glucocorticoids and 5-hydroxytryptamine, the latter in moderate exercise only, also increase. This further increases catecholamines release. This results in increased activation of D_1-receptors and α_1-adrenoceptors, in the prefrontal cortex, which dampens all neural activity, thus inhibiting central executive performance. However, activation of β- and α_1-adrenoceptors can positively affect signal detection in the sensory cortices, hence performance of perception/attention and autonomous tasks can be facilitated. Animal studies also show that during long-duration, moderate exercise and heavy exercise, NE activation of β-adrenoceptors releases cAMP, which modulates the signaling and trafficking of the BDNF receptor Trk B, which facilitates long-term potentiation.

39 Keywords: adrenoceptors; BDNF; central executive; locus coeruleus; nucleus tractus solitarii;
40 prefrontal cortex.

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1. Introduction

In a recent review [1], we examined the efficacy of the catecholamines hypothesis [2] in providing an underlying rationale for empirical research results concerning the acute exercise-cognition interaction effect. We concluded that the hypothesis, as it stands, could not account for (a) improvements in cognition during exercise intensities and/or durations, which did not induce increases in plasma concentrations of catecholamines; (b) the failure to unequivocally demonstrate an inverted-U effect, with respect to cognitive testing at rest, and during moderate and heavy exercise; (c) improvements in cognitive performance following heavy exercise that has been shown in some research; (d) nor why different task types appear to be affected differently. Moreover, in line with most previous narrative [3-5] and meta-analytic reviews [6-10], we also concluded that the underlying mechanisms concerning (a) the interaction between peripherally circulating catecholamines and brain concentrations during exercise; (b) the effects of different exercise intensities x durations on concentrations of brain catecholamines and how these interact with different cognitive tasks; and (c) the interaction between brain catecholamines, glucocorticoids, brain derived neurotrophic factor (BDNF) and 5-hydroxytryptamine (5-HT), also known as serotonin, are not adequately expressed.

It is my contention that many of these issues can be cleared by drawing on animal research, from epigenetic, neurochemical and psychophysiological perspectives, into a) feedback via the vagal/nucleus tractus solitarii (NTS) pathway during acute exercise; b) effects of different exercise intensities x durations on concentrations of brain catecholamines, glucocorticoids,

BDNF and 5-HT; c) the roles of feedforward and feedback between brain regions regulating catecholamines, glucocorticoid and 5-HT release; d) the interaction between acute stress, including exercise, and brain catecholamines, glucocorticoids and BDNF; and e) the interaction between brain catecholamines, glucocorticoids, BDNF and 5-HT during cognition using different task types.

1.1. Catecholamines hypothesis

Cooper [2] was the first to posit a neuroendocrine hypothesis, the catecholamines hypothesis, for the acute exercise-cognition interaction effect. He pointed to evidence of increased peripheral concentrations of norepinephrine (NE) during exercise [11] and claimed that, although catecholamines do not readily cross the blood-brain barrier, if circulating concentrations were high, the blood-brain barrier would be compromised. Cooper claimed that NE crossing the blood-brain barrier would lead to increases in concentrations in the reticular formation and hence an increase in arousal, which would benefit cognition at moderate concentrations (during moderate intensity exercise) but have a negative effect when concentrations rose to higher levels (during heavy exercise). He stated that, at low levels of NE, brain activity is limited because the appropriate sequence of neuronal activation cannot be obtained as a result of neurons being at such a low level of excitation that they cannot be stimulated to an adequate level of summation. Hence cognitive performance is poor. Moderate intensity exercise and the resultant increase in brain NE means that excitation levels are such that summation is facilitated and the appropriate sequence occurs. However, as NE concentrations rise still further, neurons which are not part of the pattern are also activated, producing neural ‘noise’ and hence poor cognitive performance (see [1] for more detail). This supported the

claims of Yerkes and Dodson [12] that stress would induce an inverted-U effect on performance of many tasks.

Although the inverted-U effect of acute exercise on cognition is often claimed by authors, narrative [3-5] and meta-analytic reviews [6-9] show that the empirical evidence does not fully support this. Therefore, in the following sections, I examine what animal studies show us concerning the effects of low intensity; short to moderate duration (SMD), moderate intensity; long duration (LD), moderate intensity; and heavy acute exercise on brain concentrations and activity of NE and dopamine (DA), and why an unequivocal inverted-U effect is not forthcoming.

2. Low intensity, and short to moderate duration, moderate intensity exercise

Defining exercise intensities has been a contentious issue in acute exercise-cognition interaction research ever since Tomporowski and Ellis' [13] seminal paper. Few studies have examined the effect of mild or low intensity exercise. The majority of such studies demonstrated no significant effect, however some studies do show positive effects [14,15]. I will return to this issue later. Based on Borer's [16] definitions of exercise intensity, in previous studies my colleagues and I [1,9,17] interpreted moderate intensity exercise as being ≥ 40% maximum volume of oxygen uptake ($\dot{V}O_{2MAX}$) but < 80% $\dot{V}O_{2MAX}$. Borer's definition was determined by endocrinal changes such as increased plasma concentrations of NE, epinephrine (Epi), and lactate, although she set her lowest intensity at 50% $\dot{V}O_{2MAX}$. We lowered it to 40% as several acute exercise-cognition studies have demonstrated facilitation effects using an intensity of 40% $\dot{V}O_{2MAX}$ or equivalent [18.19]. Moreover, based on Hodgetts et al.'s [20] research, we interpreted SMD as being 10-20 mins, possibly as long as 30 mins depending on individuals' fitness levels.

Longer durations result in further increases in catecholamines and lactate [20]. Fittingly, these durations and intensities are the most common in the acute exercise-cognition literature.

Modifications of the catecholamines hypothesis [21,22] stated that SMD, moderate intensity exercise would need to reach the point where peripherally circulating plasma catecholamines begin an exponential rise, known as the catecholamines threshold (CT) [23] before having a positive effect on cognition. This makes sense as increases in peripherally circulating Epi and NE would activate β-adrenoceptor chemoreceptors on the vagus nerve (see [24] for a review). The excitatory neurotransmitter glutamate mediates synaptic communication between the vagal afferents and the NTS, allowing noradrenergic cells in the NTS, which project to the locus coeruleus (LC), to stimulate NE synthesis and release to other parts of the brain [25]. Moreover, Soya and associates [26,27], experimenting with rodents, have shown that acute exercise above the lactate threshold (LT: beginning of an exponential rise in blood lactate concentrations), which occurs at about the same time as the CT [23], activates A1 and A2 noradrenergic neurons in the NTS, as demonstrated by increased c-Fos expression (however, see below for an important additional finding by [26]).

Rodent studies have also shown that acute exercise induces c-Fos expression in adrenergic C1 neurons in the rostral ventrolateral medulla [28,29]. C1 neurons project to the LC [30,31] and Holloway et al. [32] claimed that these C1 neurons, which produce glutamatergic excitatory postsynaptic currents [33,34], are the most likely to establish glutamatergic synapses with the LC, although A1 and A2 neurons also innervate the LC [35,36]. C1, A1 and A2 neurons also have an indirect effect on the LC via projections to the hypothalamus [31,36], which in turn projects to the LC [37,38], the main source of NE in the brain. One would expect that this will

induce increased synthesis and release of NE to the prefrontal cortex (PFC) and other brain regions involved in cognition, via the dorsal bundle of the noradrenergic pathway (see Figure 1).

Insert Figure 1 about here

A1, A2, A5 and A6, LC neurons also project to the ventral tegmental area (VTA) [39], where they activate α_1-adrenoceptors, which induce enhanced glutamate release thus potentiating the firing of DA neurons. Also, these noradrenergic neurons, along with the adrenergic C1 neuron, project to the retrorubral field (RRF) in the reticular formation and stimulate DA activation there [36] (see Figure 2). The VTA and RRF are brain regions involved in cognitive functioning, with projections to the frontal cortex and cingulate cortex.

Insert Figure 2 about here

Given the role of the vagal/NTS pathway, it is of no surprise to find that rodent studies show evidence of acute exercise-induced increases in brain concentrations of NE and DA (see [40,41] for reviews), the NE metabolite 3-methoxy 4-hydroxyphenylglycol (MHPG), and the DA metabolites 3,4-dihydroxyphenylacetic acid (DOPAC) and 4-hydroxy 3-methoxyphenylacetic acid, also known as homovanillic acid (HVA), suggesting increased turnover of DA and NE during exercise. Increased concentrations of MHPG have been found in most brain regions [35], while increased concentrations of DOPAC and HVA have been shown, particularly in the brainstem and hypothalamus [42,43].

Taken together, these findings strongly support the claims that acute exercise, at or above CT, is crucial to acute exercise-induced facilitation of cognition. However, a recent meta-analytic study [10] showed that although cognition immediately post-CT, LT and ventilatory threshold (VT: the point at which ventilatory carbon dioxide shows a greater increase than ventilatory oxygen [44], which occurs at about the same time as CT and LT [23]) demonstrated a

moderate mean effect size, so did exercise below the thresholds. Moreover, there was no significant difference between effect sizes, thus presenting a major challenge to the catecholamines hypothesis.

In several studies, based on claims of Mason [45,46], my colleagues and I [1,9,10] have tried to explain such findings by arguing that if the individual perceives the situation as being unpredictable and/or one in which he/she is not in control, higher centers of the brain, e.g. PFC and limbic system, may initiate activation of the sympathoadrenal system, which will induce increased synthesis and release of NE and DA in the brain. Indeed, Cooper [2] made similar claims based on the work of Rushmer et al. [47]. He argued that feedforward, due to anticipation of undertaking exercise, led to the initiation of the sympathoadrenal system by the hypothalamus, which would induce increased activation of the reticular formation and hence higher levels of arousal. Evidence does exist to show that the PFC and limbic system [48,49] do project to the hypothalamus, which can result in the release of NE from neurons in the lateral tegmental field. Although these are part of the noradrenergic ventral bundle and serve the brainstem and hypothalamus rather than the PFC or hippocampus, areas of the brain involved in cognition and memory, there are connections between the hypothalamus and LC [37,38]. These projections would result in the release of NE to the PFC and hippocampus by the LC, thus affecting working memory, learning and long-term memory. Moreover, there are also connections from the PFC [50,51] and the amygdala [38,52] to the LC, which would also initiate release of NE to the PFC, via the dorsal bundle of the noradrenergic pathway, thus aiding cognition. However, one must question the extent to which undertaking SMD, moderate intensity exercise would be perceived as stressful by participants, therefore questions arise as to whether these processes would be

initiated. As a result, observation of the rodent literature on acute exercise-induced neural plasticity led me to propose a more likely explanation [53].

Earlier, we saw that rodent studies have shown that acute exercise above LT, and hence CT, induces c-Fos expression in A1 and A2 noradrenergic neurons in the NTS [26,27], however Ohiwa yet al. [26] also demonstrated that exercise below LT could induce similar changes. Activation of the NTS at sub-LT/CT intensities is extremely unlikely to have been the result of circulating plasma catecholamines activating β-adrenoceptors on the vagus nerve. However, information from mechanoreceptors, or more accurately stretch receptors, in the heart and lungs, is fedback to the NTS via the vagus nerve [54-56]. Similarly, arterial baroreceptors provide feedback, concerning blood pressure, to the NTS via the glossopharyngeal and vagus nerves [57]. Heart rate, tidal volume and blood pressure begin to increase immediately that exercise begins [58], 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. Thus, it is not surprising to see c-Fos expression in A1 and A2 neurons in the NTS prior to CT.

These results from rodent studies show that both sub-CT and supra-CT exercise induces the initiation of transcription of NE neurons. We should note that although sub-LT exercise induced increased c-Fos expression in A1 and A2 neurons, supra-LT exercise demonstrated significantly greater expression [26]. Nevertheless, it would appear that receptors other than β-adrenoceptors, induce the synthesis and release of NE by the LC during acute exercise and this provides a strong theoretical base for sub-CT, SMD, moderate intensity exercise facilitating cognitive performance. It also highlights the need for more research into the effects of mild or

low intensity acute exercise on cognition, with particular reference to the most beneficial intensity x duration necessary to induce facilitation.

2.1. Interaction between task type, short to moderate duration, moderate intensity exercise and underlying mechanisms

In previous reviews [17,59] and meta-analyses [9,10,17], we have included four different task types: - central executive, perception/attention and short-term memory, learning/long-term memory and autonomous tasks. Central executive tasks are part of what Baddeley [60] termed working memory. According to Baddeley, working memory consists of three separate but inter-dependent parts, the central executive mechanism, and two short-term memory systems, the phonological loop and the visuospatial sketch pad. The phonological loop is responsible for the encoding of acoustic and verbal information. The visuospatial sketchpad has the same role as the phonological loop except that it processes visual and visuospatial information. The role of the central executive is to oversee and control the whole process. It ensures that there is integration of perceptual input and comparison of the present situation (held in short-term memory) with recalled information from long-term memory. Miyake et al. [61] described the central executive process as involving several functions, which include shifting between tasks or mental sets; updating and monitoring working memory representations, which involves the removal of redundant information and replacing it with new, relevant information; inhibition of prepotent responses; planning; and the coordination of multiple tasks. Leh et al. [62] provided other examples, e.g. abstract thinking, cognitive flexibility and selecting relevant sensory information. Central executive processes are vital to everyday tasks such as problem solving, planning your day, managing one's money and driving a car. Moreover, Positron Emission Tomography and functional Magnetic Resonance Imaging research has shown that central executive tasks

primarily activate the PFC but also draw on information recalled from other parts of the brain (see [62,63] for reviews).

Perception/attention tasks are as those tasks which require focusing on and/or identifying relevant stimuli then carrying out a comparatively simple, pre-determined response [59]. These are tasks such as simple and choice reaction time, visual search and coincidence anticipation. In general, the first stage of such tasks requires activation of the specific sensory region or regions involved. Information extracted from the sensory cortices is passed to the sensory association areas and PFC where it is integrated and interpreted. The level of integration and interpretation varies between tasks but does not include any of the processes involved in working memory tasks. As such, these tasks are generally thought of as being more simple than working memory tasks. We should note that perception and attention are issues in all types of task, including central executive tasks, which are top-down tasks. Top-down, perceptual ability tasks are controlled by the dorsal frontoparietal attention network [64]. An example of such tasks would be tasks where there is competition for attention [65]. In the "bottom-up" tasks, which have been commonly used in acute exercise-cognition research, such as simple and choice reaction time, the dorsal frontoparietal attention network does not appear to affect behavior [66]. Similarly, when short-term memory is part of working memory and plays an important role in central executive task performance, the prefrontal cortex and the the dorsal frontoparietal attention network are activated [67]. However when tasks require simply acquiring the information and immediately recalling it, they are processed similar to perceptual ability tasks or rather "bottom-up" perceptual tasks.

Autonomous tasks are well-learned skills, in this case cognitive skills. They require little processing and are carried out automatically. While they may have been learned explicitly and,

during learning, required activation of the PFC and parietal cortex, thus demonstrating top-down control, with practice the roles of the prefrontal and parietal cortices diminish [68-70] and the sensory cortices and their association areas take control. Thus, a well-learned perception/attention task may respond slightly differently to exercise than a less well-learned task. However, automaticity can also apply to central executive tasks [71], with the PFC showing reduced activation due to practice [72-73], but there is an increase in sensorimotor cortex activity [74]. Thus autonomous central executive tasks can act like a perception/attention task.

I have not separated learning and long-term memory tasks because learning requires the formation of long-term memory stores. As most acute exercise-learning/long-term memory studies have been undertaken with heavy exercise, and there is strong evidence regarding the underlying processes which indicate that heavy exercise may be necessary for learning to take place, we will examine these tasks in 3.3.

Before examining the effects of acute exercise on each different task-type, we need to comment on the effect of the dependent variable in central executive tasks. Although SMD, moderate intensity, acute exercise has been shown to induce improved cognitive performance, this is affected by the dependent variable. My colleagues and I have shown that when speed is the dependent variable, there is a significant improvement in performance, however when accuracy is the dependent variable, results tend to be non-significant [9,17]. McMorris and Hale [9] claimed that this was due to the fact that most of the tasks, in which accuracy was measured, were in fact tasks designed to test efficiency through speed of performance, e.g. flanker task [75], Stroop color test [76], Go/No Go test [77].

All of the tasks, with the possible exception of learning/long-term memory, benefit from LC stimulation of the reticular formation, which improves attention and vigilance [78]. This was

the major part of Cooper's [2] original hypothesis for acute, moderate intensity exercise-induced facilitation of cognitive performance. However, more recent rodent and non-human primate studies into the interaction between a variety of stressors and cognition have shown that the PFC is also directly affected by increased NE and DA synthesis and release [79-80]. This is beneficial to all of the tasks but especially central executive tasks and may account for the fact that central executive tasks show effect sizes in the moderate to high category during and following SMD moderate intensity exercise, while the other tasks demonstrate low to moderate effect sizes [9,10].

Animal studies have shown that when stress rises to a moderate level, brain NE and DA concentrations increase and there is increased firing of the high affinity α_{2A}-noradrenergic receptors by NE [81], which increases the strength of neural signaling in the preferred direction by inhibiting second messenger cyclic adenosine monophosphate (cAMP) activation [82]. Similarly, the high affinity dopaminergic D_1-receptors are activated by DA, which dampens the 'noise' by inhibiting firing to non-preferred stimuli [83]. So DA and NE, working together, improve the signal to 'noise' ratio. This is particularly positive for the central executive tasks as they require a great deal of PFC activation [62,63] but, as we saw above, the other tasks also involve some PFC activation. Learning/long-term memory, however, uses different processes and, during SMD, moderate intensity exercise, may only benefit from increased reticular formation activation aiding attention to incoming information in the acquisition phase of encoding.

3. Long-duration, moderate intensity and heavy exercise

In the previous section, we were concerned with SMD, moderate intensity exercise, in which catecholamines concentrations remain moderate. However, evidence exists to show that with LD, moderate intensity exercise, plasma catecholamines concentrations begin to rise after ~30 mins [20]. In fact, Chmura et al. [84] actually demonstrated significant increases after 10 mins for a group who exercised at a workload designed to elicit an intensity of 110% LT and at 20 mins for a group who exercised at 75% LT. The issue is exacerbated by the fact that after ~45 mins duration there also appears to be increased plasma cortisol concentrations [85]. Furthermore, LD, moderate intensity exercise also induces increases in brain concentrations of 5-HT in animal studies [40,41,86-90]. The net results of these effects during LD, moderate intensity exercise means that effects are more similar to those induced by heavy exercise than those by SMD, moderate intensity exercise.

Moreover, Blomstrand et al. [91] examined the brain uptake of tryptophan, the precursor of 5-HT, during prolonged exercise (3 h at 200 ± 7 W, on a cycle ergometer) in humans, by calculating the arterial to internal jugular venous difference multiplied by plasma flow. They found large increases in cerebral uptake, which they, not unreasonably, assumed meant increased synthesis and release of 5-HT in the brain. The authors claimed that the increases in cerebral uptake were a direct result of the action of unbinding tryptophan from albumin as a result of the organism's use of fat as the main energy supply, thus easing the crossing of the blood-brain barrier for tryptophan. Fat rather than carbohydrates is recruited mostly in sub-maximal, LD exercise. In shorter intensity, heavy exercise, lactate restricts the transport of free fatty acids in the blood [92] as does α-adrenoceptor action [93], therefore there are no available free fatty acids to unbind tryptophan from albumin.

We are defining heavy exercise as being ≥ 80% $\dot{V}O_{2MAX}$ based on the fact that at this intensity, NE and Epi plasma concentrations are very high. Moreover, in humans, there are also increases in plasma concentrations of the hypothalamic-pituitary-adrenal (HPA) axis hormones cortisol and adrenocorticotrophin hormone (ACTH) in plasma [94,95]. Concentrations of these HPA axis hormones and their precursor corticotropin releasing factor (CRF) affect cognition in an inverted-U fashion [96]. Their effect on memory consolidation is well documented [96] but, as we will see below, by interacting with DA and NE they also have effects on many cognitive processes.

In the following sub-sections, I discuss how brain catecholamines, glucocorticoids and 5-HT interact to affect cognition during LD, moderate intensity and heavy intensity exercise. I also discuss the interaction between catecholamines and BDNF with respect to learning and long-term memory.

3.1. Central executive tasks

Animal studies have shown that when stress levels are high, as during LD, moderate duration and heavy exercise, DA and NE concentrations become very high. Feedback to the LC, via the vagal/NTS pathway, induces the synthesis and release of NE. This can be exacerbated by the activity of CRF, which also stimulates NE release [97]. High concentrations of NE activate the lower affinity α_1- and β-adrenoceptors [81] in the PFC. Furthermore, within the PFC, glucocorticoids further stimulate activation of α_1-adrenoceptors and D_1-receptors [98]. During LD, moderate intensity exercise, activation of the 5-HT_{1A} and 5-HT_{2A} serotonergic receptors in the LC facilitate NE release, while activation of these receptors in the medial PFC stimulates release of DA from the VTA [99]. Thus in both LD, moderate intensity and heavy exercise, there are high concentrations of NE and DA. The result is that activation of α_1-adrenoreceptors reduces

neuronal firing, while increased stimulation of D_1-receptors and β-adrenoceptors induces even greater activity of the second messenger, cAMP, which dampens all neuronal activity, thus weakening the signal to 'noise' ratio [80]. Hence, during LD, moderate intensity and heavy exercise, we expect to see cognitive performance of central executive tasks inhibited and this is confirmed by reviews and meta-analyses [1,6,9,100]. However, the situation is more complex than that and some central executive processes are actually enhanced by high levels of stress [80].

Eagle et al. [101] (as cited by [80]) showed that performance of the stop signal task by rats was facilitated by increased activation of β-adrenoceptors, while attentional set shifting has been found to benefit from activation of α_1-receptors [102,103]. Why this occurs is difficult to explain. The stop signal task requires stopping an ongoing movement and is thought to be controlled by a "fronto-basal ganglia network in the right hemisphere", consisting of the pre-supplementary motor area, inferior frontal cortex, basal ganglia and primary motor cortex [104] (p. e59). Attentional set shifting requires the participant to switch between stimulus-response sets when the stimulus changes [105]. The key brain areas involved appear to be the dorsolateral PFC and the posterior parietal cortex [106]. During LD, moderate intensity and heavy exercise, these tasks are affected in a similar way to perception/attention tasks (see 3.2). This is not surprising given the comparatively small involvement of the PFC and the simplicity of the tasks. In fact, both tasks appear to be affected differently by stress when there is competition from other stimuli and responses. In these situations, they are affected in the same way as other central executive tasks [104,107].

3.2. Perception/attention and short-term memory tasks, and autonomous tasks

As we saw in 2.1, the first stage of perception/attention and short-term memory tasks requires activation of the specific sensory region or regions involved. Information extracted from the sensory cortices is passed to the sensory association cortices and PFC where it is integrated and interpreted. The level of integration and interpretation varies between tasks but is less demanding than the processes involved in central executive tasks. Similarly, autonomous tasks are controlled by the sensory cortices and their association areas, especially the sensorimotor cortex [74]. Stress research with animals has shown that in contrast to the PFC, high concentrations of NE activating α_1- and β-adrenoceptors can positively affect signal detection [108,109]. Moreover, research has also shown that the effect can be stimulated by CRF acting on the LC-NE system. CRF causes tonic firing of LC-NE neurons, which results in suppression of somatosensory signal transmission within the somatosensory thalamus and cortex [110]. This appears to reduce detectability of low-intensity stimuli without affecting high-intensity stimuli [111,112]. At this moment in time, empirical research supports claims that LD, moderate and heavy exercise have positive effects on autonomous tasks but findings are somewhat equivocal for perception/attention and short-term memory tasks [1,9]. However, there are a limited number of studies that have examined the effect of LD, moderate intensity and heavy exercise on cognition in such tasks.

3.3. Learning/long-term memory tasks

Before examining the effect of LD, moderate intensity and heavy exercise on learning/long-term memory tasks, we need to outline the processes involved in learning and the development of long-term memory. There are three stages to learning. The initial stage is called encoding and it consist of two sub-stages, acquisition and consolidation. Acquisition is really part of short-term memory and refers to the registering and sensory analysis of information.

Consolidation is the creation of a stronger representation and takes place over a period of time. The second stage is storage, which is the creation and maintenance of a permanent record in long-term memory. The final stage, retrieval, refers to using the stored information to recall facts. Memory can be declarative, also known as explicit memory, which is consciously encoded and recalled: or non-declarative, also known as implicit memory, which refers to sub-consciously or implicitly learned information. Consolidation of declarative information appears to be primarily undertaken by the hippocampus and requires the process of long-term potentiation (LTP), the strengthening of synaptic connections between neurons. Processes of consolidation in implicit memory are less well understood. The basal ganglia are thought to be important in implicit learning [113,114], although there are some common brain activations during explicit and implicit learning [115]. Despite this, Yang and Li [115] concluded that distinct neural mechanisms serve explicit versus implicit learning/memory.

Consolidation, particularly of explicit memory, is generally divided into two phases, early and late. Early-LTP (E-LTP) lasts for about 4–6 h, while late-LTP (L-LTP) has a duration of more than 4–6 h [116]. During LD, moderate intensity exercise, nitric oxide (NO) is released from the endothelium [117], where it is produced from the amino acid L-arginine, with cyclic guanosine monophosphate (cGMP) as the second messenger. NO signaling is mostly mediated by soluble guanylyl cyclase (sGC) [118]) and this leads to the activation of cGMP-dependent protein kinase (PKG). PKG, in turn, enhances neurotransmitter release [119,120] and this forms the basis of E-LTP. The role of catecholamines in LTP, however, is seen in L-LTP. When heavy or LD, moderate intensity exercise induces high concentrations of NE in the hippocampus, it activates β-adrenoceptors, which are GTP-binding proteins and stimulate cAMP activation. Acute exercise also results in increases in serum or plasma BDNF concentrations in humans

403 [121-127], while animal studies have demonstrated strong evidence for acute exercise inducing
404 increased BDNF and/or BDNF messenger ribonucleic acid (mRNA) expression in the brain, in
405 particular in the hippocampus [128-133]. It is the interaction between BDNF and NE via cAMP
406 activity that is vital for L-LTP.

407 The synaptic actions of BDNF are 'gated' or regulated by cAMP, as it modulates the
408 signaling and trafficking of the BDNF receptor tropomyosin-related kinase B (Trk B) [134,135].
409 The binding of BDNF to Trk B, initiates a number of intracellular signaling cascades, including
410 calcium/calmodulin kinase II and mitogen-activated protein kinase, resulting in the
411 phosphorylation of cAMP-response element binding protein (CREB) [136-138]. The whole
412 process modulates synaptic transmission in a lasting manner by modifying synaptic protein
413 composition via local protein synthesis [138], thus facilitating synaptic transmission.

414 As can be seen from the above, the cascade initiated by NE activation of β-adrenoceptors
415 and BDNF binding to Trk B occurs downstream. This has led to some speculation concerning the
416 timing of exercise with regard to the acquisition and consolidation phases of LTP. This is an area
417 in which there is insufficient research. It may be better to exercise during acquisition, as the
418 effects of the cascade will occur after exercise, i.e. during consolidation. However, exercise
419 during consolidation may be better as consolidation can take place well after acquisition.

420 3.3.1. Implicit long-term memory.

421 So far we have been discussing research undertaken on explicit or declarative long-term
422 memory tasks. However, LTP occurs also during implicit learning [139,140], but there are some
423 differences. The hippocampus is thought to play a part in the implicit learning of some but, not
424 all, tasks [141], but the basal ganglia, in particular the striatum, are heavily involved in many
425 implicit learning tasks [113-115]. While β-adrenoceptors are present in the basal ganglia [142]

and may regulate BDNF/Trk B activity, the dopaminergic system is dominant and high concentrations of DA have been shown to aid learning in this region [143]. Like β-adrenoceptors, dopaminergic D_1-receptors are GTP-binding proteins, with cAMP as the second messenger. cAMP activates protein kinase A (PKA), which, in turn, activates CREB and thus LTP occurs [144].

4. Resistance exercise

The exercise protocols examined in the McMorris et al. [1] study were running or cycling based. However, recently there has been interest in the effect of resistance exercise on cognition. A number of studies have shown positive effects of acute resistance exercise, of sub-maximal (< 80% maximum repetitions) intensity, on performance of central executive tasks [100, 145,146], while one study [147] found positive effects on long-term memory following maximal isometric and dynamic contractions. I decided to include resistance exercise separately as the nature of the activity is different to the cycling and running used in most studies. However, observation of the human literature on the effects of resistance exercise on plasma and serum concentrations of Epi, NE and cortisol suggests similar responses to those found following running and cycling [148,149], therefore these results are not surprising.

5. Conclusion

Animal studies show that during SMD, moderate intensity exercise, NE is released by the LC as the result of feedback from the NTS via stretch reflexes, baroreceptors and, post-CT, β-adrenoceptors on the vagus nerve. Feedback, via receptors other than chemoreceptors, explains improvements in cognition during exercise intensities and/or durations, which did not induce increases in plasma concentrations of catecholamines, something for which the earlier versions of the catecholamines hypothesis could not account. NE release activates the reticular system,

thus increasing arousal levels, which aids vigilance and attention. Similarly, research with animals, which has examined the interaction between stress and activation of α_{2A}-adrenoceptors and D_1-dopaminergic receptors in the PFC, shows that these receptors interact to increase the signal to 'noise' ratio. This provides a viable explanation as to why central executive tasks demonstrate larger positive effect sizes during SMD, moderate intensity exercise than other task types, which depend less on PFC activation. Thus partially explaining why different task types appear to be affected differently

Animal studies employing high levels of stress explain the greater negative effects of LD, moderate intensity and heavy exercise on central executive tasks and go some way to enlightening our knowledge of the effects of these levels of exercise on autonomous and perception/attention tasks. In the PFC, increased activation of D_1-receptors and α_1-adrenoceptors dampens all neural activity, thus reducing the signal to 'noise' ratio and inhibiting central executive performance. In the sensory cortices, however, activation of β- and α_1-adrenoceptors can positively affect signal detection [108,109], hence performance is facilitated, although the empirical data on perception/attention tasks are less convincing than those for autonomous tasks [1]. This explains the failure to unequivocally demonstrate an inverted-U effect, with respect to cognitive testing at rest, and during moderate and heavy exercise; and why improvements in cognitive performance following heavy exercise have been shown in some research;

Animal studies also demonstrate the interaction between catecholamines, glucocorticoids and 5-HT during LD, moderate intensity and heavy exercise, which appears to further stimulate catecholamines release. Finally, animal studies show how catecholamines and BDNF interact during learning and LTP in both declarative and implicit memory tasks, particularly the former.

Undoubtedly, examination of the animal literature provides explanations of how sub- and supra-CT, acute exercise can facilitate cognitive performance; why central executive tasks benefit most from SMD, moderate intensity exercise; how autonomous tasks are facilitated by LD, moderate exercise and heavy exercise; why central executive tasks are particularly vulnerable to LD, moderate exercise and heavy exercise; and how LD, moderate exercise and heavy exercise aid learning. Nevertheless, we are still left with an incomplete picture with regard to perception/attention and short-term memory tasks during LD, moderate intensity exercise and heavy exercise. The lack of research into the effects of LD, moderate intensity exercise and heavy exercise is surprising given that it is in such situations that decisions have to be made by the military, firefighters and mountain rescuers not to mention sports-performers.

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843

844 **Figure legends**

845 Figure 1. Schematic representation of the noradrenergic pathway (from McMorris T, Turner A,
846 Hale BJ, Sproule J. Beyond the catecholamines hypothesis for an acute exercise-cognition
847 interaction: a neurochemical perspective. In: McMorris, T, editor. Exercise-cognition interaction:
848 neuroscience perspectives, New York: Academic Press; 2016, p 71. Published with permission.)
849 Figure 2. Schematic representation of the dopaminergic pathway (from McMorris T, Turner A,
850 Hale BJ, Sproule J. Beyond the catecholamines hypothesis for an acute exercise-cognition
851 interaction: a neurochemical perspective. In: McMorris, T, editor. Exercise-cognition interaction:
852 neuroscience perspectives, New York: Academic Press; 2016, p 71. Published with permission.)
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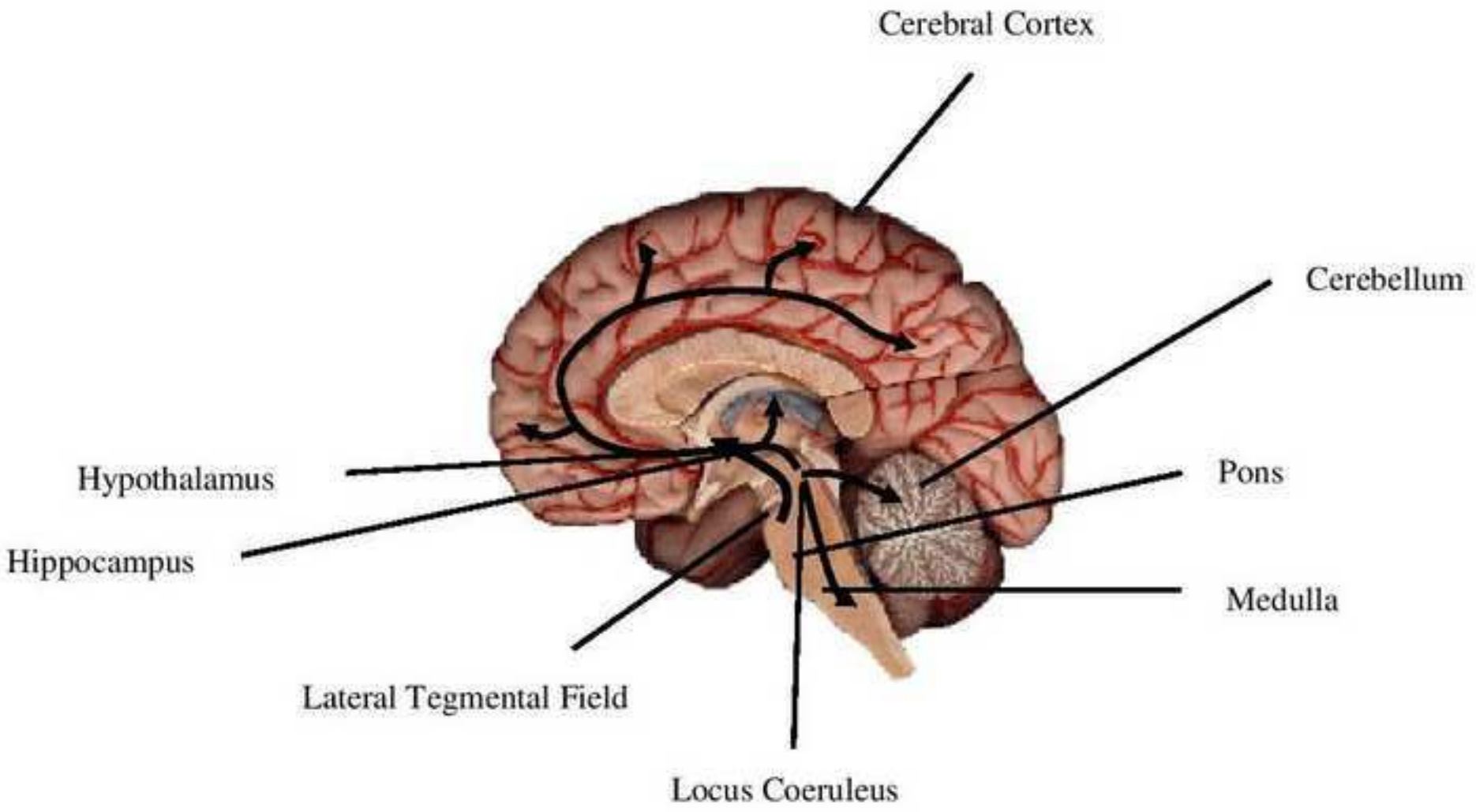

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