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

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

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

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

3.3.1. Implicit long-term memory.

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

References

[1] McMorris T, Turner A, Hale BJ, Sproule J. Beyond the catecholamines hypothesis for an acute exercise-cognition interaction: a neurochemical perspective. In: McMorris, T, editor. Exercise-cognition interaction: neuroscience perspectives, New York: Academic Press; 2016, p 65-104.

[2] Cooper CJ. Anatomical and physiological mechanisms of arousal with specific reference to the effects of exercise Ergonomics 1973;16:601-9.

[3] Best JR. Effects of physical activity on children's executive function: contributions of experimental research on aerobic exercise Dev Rev 2010;30:331-51.

[4] McMorris T, Graydon J. The effect of incremental exercise on cognitive performance Int J Sport Psychol 2000;31:66–81.

493 [5] Tomporowski PD. Effects of acute bouts of exercise on cognition Acta Psychol
494 2003;112:297-324.
495 [6] Chang YK, Labban JD, Gapin JI, Etnier JL. The effects of acute exercise on cognitive
496 performance: A meta-analysis Brain Res 2012;1453:87-101.
497 [7] Etnier JL, Salazar W, Landers DM, Petruzzello SJ, Han M, Nowell P. The influence of
498 physical fitness and exercise upon cognitive functioning: a meta-analysis *J* Sport Exerc Psychol
499 1997;19:249–77.
500 [8] Lambourne K, Tomporowski PD. The effect of acute exercise on cognitive task performance:
501 A meta-regression analysis Brain Res 2010;1341:12-24.
502 [9] McMorris T, Hale BJ. Differential effects of differing intensities of acute exercise on speed
503 and accuracy of cognition: a meta-analytical investigation Brain Cogn 2012;80:338-51.
504 [10] McMorris T, Hale BJ. Is there an acute exercise-induced physiological/biochemical
505 threshold which triggers increased speed of cognitive functioning? A meta-analytic investigation
506 J Sport Health Sci 2015;4:4-13.
507 [11] Vendsalu A. Studies on adrenaline and noradrenaline in human plasma Acta Physiol Scand
508 1960;49:1-123.
509 [12] Yerkes RM, Dodson JD. The relation of strength of stimulus to the rapidity of habit
510 formation J Comp Neurol Psychol 1908;18:459-82.
511 [13] Tomporowski PD, Ellis NR. Effects of exercise on cognitive processes: a review Psychol
512 Bull 1986:99:338–46.
513 [14] Kamijo K, Hayashi Y, Sakai T, Yahiro T, Tanaka K, Nishihira Y. Acute effects of aerobic
514 exercise on cognitive function in older adults. J Gerontol Psychol Sci 2009:64B:356–63.

515 [15] Potter D, Keeling D. Effects of moderate exercise and circadian rhythms on human
516 memory. J Sport Exerc Psychol 2005:27:117-25
517 [16] Borer, KT, Exercise endocrinology. Human Kinetics: Champaign, IL; 2003.
518 [17] McMorris T, Sproule J, Turner A, Hale BJ. Acute, intermediate intensity exercise, and
519 speed and accuracy in working memory tasks: a meta-analytical comparison of effects Physiol
520 Behav 2011;102:421-8.
521 [18] Brisswalter J, Arcelin R, Audiffren M, Delignières D. 1997. Influence of physical exercise
522 on simple reaction time: effect of physical fitness. Percept Mot Skills 1997:85:1019-27.
523 [19] Joyce J, Graydon J, McMorris T, Davranche K. The time course effect of moderate intensity
524 exercise on response execution and response inhibition. Brain Cogn 2009:71:14-9.
525 [20] Hodgetts V, Coppack SW, Frayn KN, Hockaday TDR. Factors controlling fat mobilization
526 from human subcutaneous adipose-tissue during exercise J Appl Physiol 1991;71:445–51.
527 [21] Chmura J, Nazar H, Kaciuba-Uścilko H. Choice reaction time during graded exercise in
528 relation to blood lactate and plasma catecholamine thresholds Int J Sports Med 1994;15:172-6.
529 [22] McMorris T, Myers S, MacGillivary WW, Sexsmith JR, Fallowfield J, Graydon J, Forster
530 D. Exercise, plasma catecholamine concentration and decision-making performance of soccer
531 players on a soccer-specific test J Sport Sci 1999;17:667-76.
532 [23] Podolin DA, Munger PA, Mazzeo RS. Plasma-catecholamine and lactate response during
533 graded-exercise with varied glycogen conditions J Appl Physiol 1991;71:1427-33.
534 [24] McGaugh JL, Cahill L, Roozendaal B. Involvement of the amygdala in memory storage:
535 Interaction with other brain systems Proc Natl Acad Sci U S A 1996;93:13508-14.

536 [25] Miyashita T, Williams CL. Epinephrine administration increases neural impulses
537 propagated along the vagus nerve: role of peripheral beta-adrenergic receptors Neurobiol Learn
538 Mem 2006;85:116-24.
539 [26] Ohiwa N, Saito T, Chang H, Omoria T, Fujikawa T, Asada T, Soya H. Activation of A1 and
540 A2 noradrenergic neurons in response to running in the rat Neurosci Lett 2006;395:46–50.
541 [27] Soya H, Mukai A, Deocaris CC, Ohiwa N, Chang H, Nishijima T, Fujikawa T, Togashi K,
542 Saito T. Threshold-like pattern of neuronal activation in the hypothalamus during treadmill
543 running: Establishment of a minimum running stress (MRS) rat model Neurosci Res
544 2007;58:341–8.
545 [28] Abbott SB, DePuy SD, Nguyen T, Coates MB, Stornetta RL. Guyenet PG. Selective
546 optogenetic activation of rostral ventrolateral medullary catecholaminergic neurons produces
547 cardiorespiratory stimulation in conscious mice. J Neurosci 2013;33:3164–77.
548 [29] Barna BF, Takakura AC, Moreira TS. Pontomedullary and hypothalamic distribution of fos-
549 like immunoreactive neurons after acute exercise in rats Neurosci 2012;212:120–30.
550 [30] Abbott SB, Kanbar R, Bochorishvili G, Coates MB, Stornetta RL, Guyenet PG. C1 neurons
551 excite locus coeruleus and A5 noradrenergic neurons along with sympathetic outflow in rats J
552 Physiol 2012;590:2897–915.
553 [31] Guyenet PG, Stornetta RL, Bochorishvili G, Depuy SD, Burke PG, Abbott SB. C1 neurons:
554 the body's EMTs Am J Physiol Regul Integr Comp Physiol 2013;305:R187–204.
555 [32] Holloway BB, Stornetta RL, Bochorishvili G, Erisir A, Viar KE, Guyenet PG.
556 Monosynaptic glutamatergic activation of Locus Coeruleus and other lower brainstem
557 noradrenergic neurons by the C1 cells in mice J Neurosci 2013;33:18792–805.

[33] DePuy SD, Stornetta RL, Bochorishvili G, Deisseroth K, Witten I, Coates M, Guyenet PG. Glutamatergic neurotransmission between the C1 neurons and the parasympathetic preganglionic neurons of the dorsal motor nucleus of the vagus J Neurosci 2013;33:1486-97.

[34] Stornetta RL, Sevigny CP, Guyenet PG. Vesicular glutamate transporter DNPI/VGluT2 mRNA is present in C1 and several other groups of brainstem catecholaminergic neurons J Comp Neurol 2002;444:191–206.

[35] Ferrucci M, Giorgi FS, Bartalucci A, Busceti CL, Fornai F. The effects of locus coeruleus and norepinephrine in methamphetamine toxicity Curr Neuropharmacol 2013;11:80-94.

[36] Rinaman L. Hindbrain noradrenergic A2 neurons: diverse roles in autonomic, endocrine, cognitive, and behavioral functions Am J Physiol Regul Integr Comp Physiol 2011;300:R222–35.

[37] Aston-Jones G, Ennis M, Pieribone VA, Nickel1 WT, Shipley MT. The brain nucleus locus coeruleus: restricted afferent control of a broad efferent network Science 1986;234:734-7.

[38] Cedarbaum JM, Aghajanian GK, Afferent projections to the rat locus coeruleus as determined by a retrograde tracing technique J Comp Neurol 1978;178:1-16.

[39] Mejías-Aponte CA, Drouin C, Aston-Jones G. Adrenergic and noradrenergic innervation of the midbrain ventral tegmental area and retrorubral field: prominent inputs from medullary homeostatic centers J Neurosci 2009;29:3613–26.

[40] Meeusen R, Piacentini MF, De Meirleir K. Brain microdialysis in exercise research Sports Med 2001;31:965-83.

[41] Meeusen R, De Meirleir K. Exercise and brain neurotransmission Sports Med 1995;20:160-85.

580 [42] Hasegawa H, Yazawa T, Yasumatsu M, Otokawa M, Aihara Y. Alteration in dopamine
581 metabolism in the thermoregulatory center of exercising rats Neurosci Lett 2000; 289:161-4.
582 [43] Meeusen R, Smolders J, Sarre S, De Meirleir K, Keizer H, Serneels M, Ebinger G, Michotte
583 Y. Endurance training effects on neurotransmitter release in rat striatum: an in vivo microdialysis
584 study Acta Physiol Scand 1997;159:335-41.
585 [44] Beaver WL, Wasserman K, Whipp BJ. A new method for detecting anaerobic threshold by
586 gas exchange J Appl Physiol 1986;60,:2020-7.
587 [45] Mason JW. A historical view of the stress field Part I J Hum Stress 1975;1:6-12.
588 [46] Mason JW. A historical view of the stress field Part II J Hum Stress 1975;1:22-36.
589 [47] Rushmer RF, Smith OA, Jr, Lasher EP. Neural mechanisms of cardiac control during
590 exertion Physiol Rev 1960;40(Suppl 4):27-34.
591 [48] Barbas H, Saha S, Rempel-Clower N, Ghashghaei T. Serial pathways from primate
592 prefrontal cortex to autonomic areas may influence emotional expression BMC Neurosci
593 2003;4:25, doi:101186/1471-2202-4-25.
594 [49] Myers B, Dolgas CM, Kasckow J, Cullinan WE, Herman JP, Central stress-integrative
595 circuits: Forebrain glutamatergic and GABAergic projections to the dorsomedial hypothalamus,
596 medial preoptic area, and bed nucleus of the stria terminalis Brain Struct Funct 2014;219:1287–
597 303.
598 [50] Jodo E, Chiang C, Aston-Jones G. Potent excitatory influence of prefrontal cortex activity
599 on noradrenergic locus coeruleus neurons Neurosci 1998;83:63-79.
600 [51] Singewald N, Philippu A. Release of neurotransmitters in the locus coeruleus Prog
601 Neurobiol 1998;56:237-67.

602 [52] Wallace DM, Magnuson DJ, Gray TS. The amygdalo-brainstem pathway: selective
603 innervation of dopaminergic, noradrenergic and adrenergic cells in the rat Neurosci Lett
604 1989;97:252-8.
605 [53] McMorris T. Re-appraisal of the acute, moderate intensity exercise-catecholamines
606 interaction effect on speed of cognition: role of the vagal/NTS afferent pathway J Appl Physiol
607 2016;in press.
608 [54] Berthoud HR, Neuhuber WL. Functional and chemical anatomy of the afferent vagal system
609 Auton Neurosci: Basic Clin 2000;85:1–17.
610 [55] Moor T, Mundorff L, Bohringer A, Philippsen C, Langewitz W, Reino ST, Schachinger H.
611 Evidence that baroreflex feedback influences long-term incidental visual memory in men
612 Neurobiol Learn Mem 2005;84:168–74.
613 [56] Mravec B. Possible involvement of the vagus nerve in monitoring plasma catecholamine
614 levels Neurobiol Learn Mem 2006;86:353–5.
615 [57] Kougias P, Weakley SM, Yao Q, Lin PH, Chen CY. Arterial baroreceptors in the
616 management of systemic hypertension Med Sci Monit 2010;16:RA1–8.
617 [58] Watson AWS. The relationship between tidal volume and respiratory frequency during
618 muscular exercise Br J Sports Med 1974;8:87-90.
619 [59] McMorris T. History of research into the acute exercise-cognition interaction: a cognitive
620 psychology approach. In: McMorris, T, editor. Exercise-cognition interaction: neuroscience
621 perspectives, New York: Academic Press; 2016, p. 1-28.
622 [60] Baddeley, AD, Working memory. Oxford University PressL New York; 1986.

623 [61] Miyake A, Friedman NP, Emerson MJ, Witzki AH, Howerter A. The unity and diversity of
624 executive functions and their contributions to complex “frontal lobe” tasks: A latent variable
625 analysis Cogn Psychol 2000;41:49-100.
626 [62] Leh SE, Petrides M, Strafella AP. The neural circuitry of executive functions in healthy
627 subjects and Parkinson's disease Neuropsychopharmacol 2010;35:70–85.
628 [63] Barbas H. Connections underlying the synthesis of cognition, memory, and emotion in
629 primate prefrontal cortices Brain Res Bull 2000;52:319-30.
630 [64] Corbetta M, Shulman GL. Control of goal-directed and stimulus-driven attention in the
631 brain. Nature Rev Neurosci 2002:3:201-15.
632 [65] Goltz D, Gundlach C, Nierhaus T, Villringer A, Müller M, Pleger B. Connections between
633 intraparietal sulcus and a sensorimotor network underpin sustained tactile attention. J Neurosci
634 2015:35:7938-49.
635 [66] Molenberghs P, Mesulam MM, Peeters R, Vandenberghe RRC. Remapping attentional
636 priorities: differential contribution of superior parietal lobule and intraparietal sulcus. Cereb
637 Cortex 2007:17:2703-12.
638 [67] Braunlich K, Gomez-Lavin J, Seger CA. Frontoparietal networks involved in categorization
639 and item working memory. NeuroImage 2015:107:146-62
640 [68] Kelly AMC, Garavan H. Human functional neuroimaging of brain changes associated with
641 practice Cereb Cortex 2005;15:1089–102.
642 [69] Prakash RS, De Leon AA, Mourany L, Lee H, Voss MW, Boot WR, Basak C, Fabiani M,
643 Gratton G, Kramer AF. Examining neural correlates of skill acquisition in a complex videogame
644 training program Front Hum Neurosci 2012;6:doi: 103389/fnhum201200115.

645 [70] Sami S, Robertson EM, Miall RC. The time course of task-specific memory consolidation
646 effects in resting state networks J Neurosci 2014;34:3982–92.
647 [71] Jimura K, Cazalis F, Stover ERS, Poldrack RA. The neural basis of task switching changes
648 with skill acquisition Front Hum Neurosci 2014;8:330, doi: 103389/fnhum201400339.
649 [72] Amemori K, Sawaguchi T. Contrasting effects of reward expectation on sensory and motor
650 memories in primate prefrontal neurons Cereb Cortex 2006;16:1002–15.
651 [73] de Wit S, Corlett PR, Aitken MR, Dickinson A, Fletcher PC. Differential engagement of the
652 ventromedial prefrontal cortex by goal-directed and habitual behavior toward food pictures in
653 humans J Neurosci 2009;29:11330–8.
654 [74] Ashby FG, Turner BO, Horvitz JC. Cortical and basal ganglia contributions to habit
655 learning and automaticity Trends Cognit Sci, 2010;14:208–15.
656 [75] Eriksen BA, Eriksen CW. Effects of noise letters upon the identification of a target letter in
657 a nonsearch task Percept Psychophys 1974;16:143–9.
658 [76] Stroop JR. Studies of interference in serial verbal reactions J Exp Psychol 1935;18:643-62.
659 [77] Donders FC. On the speed of mental processes Acta Psychol 1969; 30, 412-31.
660 [78] Kinoumura S, Larsson J, Gulyás B, Roland PE. Activation by attention of the human
661 reticular formation and thalamic intralaminar nuclei Science 1996;271:312-15.
662 [79] Arnsten AFT. Stress signalling pathways that impair prefrontal cortex structure and function
663 Nat Rev Neurosci 2009;10:410–22.
664 [80] Arnsten AFT. Catecholamine influences on dorsolateral prefrontal cortical networks Biol
665 Psychiatry 2011;69:e89–e99 doi:101016/jbiopsych201101027.
666 [81] Roth RH, Tam S-Y, Ida Y, Yang J-X, Deutch AY. Stress and the mesocorticolimbic
667 dopamine systems Ann N Y Acad Sci 1988;537:138–47.

668 [82] Deutch AY, Roth RH. The determinants of stress-induced activation of the prefrontal
669 cortical dopamine system Prog Brain Res 1990;85:367-403.
670 [83] Finlay JM, Zigmond MJ, Abercrombie ED. Increased dopamine and norepinephrine release
671 in medial prefrontal cortex induced by acute and chronic stress: effects of diazepam Neurosci
672 1995;64:619–28.
673 [84] Chmura J, Kristztofiak H, Ziemba AW, Nazar K, Kaciuba-Uścilko H. Psychomotor
674 performance during prolonged exercise above and below the blood lactate threshold Eur J Appl
675 Physiol Occup Physiol 1998;77:77-80.
676 [85] Shojaei EA, Farajov A, Jafari A. Effect of moderate aerobic cycling on some systemic
677 inflammatory markers in healthy active collegiate men Int J Gen Med 2011;4:79-84.
678 [86] Blomstrand E. A role for branched-chain amino acids in reducing central fatigue J Nutr
679 2006; 136:544S-7S.
680 [87] Fernstrom JD, Fernstrom MH. Exercise, serum free tryptophan, and central fatigue J Nutr
681 2006;136:553S-9S.
682 [88] Caperuto EC, dos Santos RV, Mello MT, Costa Rosa LF. Effect of endurance training on
683 hypothalamic serotonin concentration and performance Clin Exp Pharmacol, Physiol
684 2009;36:189-91.
685 [89] Chen HI, Lin LC, Yu L, Liu YF, Kuo YM, Huang AM, Chuang JI, Wu FS, Liao PC, Jen CJ.
686 Treadmill exercise enhances avoidance learning in rats: the role of down-regulated serotonin
687 system in the limbic system Neurobiol Learn Mem 2008;89:489-96.
688 [90] Chennaoui M, Drogou C, Gomez-Merino D, Grimaldi B, Fillion G, Guezennec CY.
689 Endurance training effects on 5-HT(1B) receptors mRNA expression in cerebellum, striatum,
690 frontal cortex and hippocampus of rats Neurosci Lett 2001;307:33-6.

691 [91] Blomstrand E, Møller K, Secher NH, Nybo L. Effect of carbohydrate ingestion on brain
692 exchange of amino acids during sustained exercise in human subjects Acta Physiol Scand
693 2005;185:203-9.
694 [92] Bülow J, Madsen J, Astrup A, Christensen NJ. Vasoconstrictor effect of high FFA/albumin
695 ratios in adipose tissue in vivo Acta Physiol Scand 1985;125:661-7.
696 [93] Gullestad L, Hallén J, Sejersted OM. Variable effects of beta-adrenoreceptor blockade on
697 muscle blood flow during exercise Acta Physiol Scand 1993;149:257-71.
698 [94] De Vries WR, Bernards NTM, De Rooij MH, Koppeschaar HPF. Dynamic exercise
699 discloses different time-related responses in stress hormones. Psychosom Med 2000:62:866-72.
700 [95] Hill EE, Zack E, Battaglini C, Viru M, Viru A, Hackney AC. Exercise and circulating
701 cortisol levels: the intensity threshold effect. J Endocrinol Invest 2008:31:587-91.
702 [96] McEwen BS, Sapolsky RM. Stress and cognitive function. Curr Opin Neurobiol
703 1995:5:205-16.
704 [97] Asbach S, Schulz C, Lehnert H. Effects of corticotropin-releasing hormone on locus
705 coeruleus neurons in vivo: a microdialysis study using a novel bilateral approach Eur J
706 Endocrinol 2001;145:359-63.
707 [98] Shansky RM, Lipps J. Stress-induced cognitive dysfunction:hormone-neurotransmitter
708 interactions in the prefrontal cortex Front Hum Neurosci 2013;7:doi: 103389/fnhum201300123.
709 [99] Dıaz-Mataix L, Scorza MC, Bortolozzi A, Toth M, Celada P, Artigas F. Involvement of 5-
710 HT_{1A} receptors in prefrontal cortex in the modulation of dopaminergic activity: role in atypical
711 antipsychotic action J Neurosci 2005;25:10831–43.

712 [100] Chang Y-K, Pan C-Y, Chen F-T, Tsai C-L, Huang C-C. Effect of resistance-exercise
713 training on cognitive function in healthy older adults: a review J Aging Phys Act 2012;20:497-
714 501.
715 [101] Eagle DM, Davies KR, Towse BW, Keeler JF, Theobald DE, Robbins TW. Beta-
716 adrenoceptor-mediated action of atomoxetine during behavioral inhibition on the stop-signal task
717 in rats Soc Neurosci Abstr 2010;508:510. Cited by Arnsten AFT. Catecholamine influences on
718 dorsolateral prefrontal cortical networks Biol Psychiatry 2011;69:e89–e99,
719 doi:101016/jbiopsych201101027.
720 [102] Bondi CO, Jett JD, Morilak DA. Beneficial effects of desipramine on cognitive function of
721 chronically stressed rats are mediated by alpha1-adrenergic receptors in medial prefrontal cortex
722 Prog Neuropsychopharmacol: Biol Psychiatry 2010;34:913–23.
723 [103] Robbins TW, Roberts AC. Differential regulation of fronto-executive function by the
724 monoamines and acetylcholine Cereb Cortex 2007;17(Suppl 1):i151–60.
725 [104] Aron AR. From reactive to proactive and selective control: developing a richer model for
726 stopping inappropriate responses Biol Psychiatry 2011;69:e55–e68,
727 doi:101016/jbiopsych201007024.
728 [105] Sawada Y, Nishio Y, Suzuki K, Hirayama K, Takeda A, Hosokai Y, Ishioka T,, Itoyamam
729 Y,, Takahashim S, Fukudam H, Morim E. Attentional set-shifting deficit in Parkinson's Disease
730 is associated with prefrontal dysfunction: An FDG-PET Study PLoS ONE 2012;7:e38498
731 doi:101371/journalpone0038498.
732 [106] Wager TD, Reading S, Jonides J. Neuroimaging studies of shifting attention: a meta-
733 analysis NeuroImage 2004;22:1679-93.

734 [107] Cools R, Barker RA, Sahakian BJ, Robbins TW. Mechanisms of cognitive set flexibility in
735 Parkinson's disease Brain 2001;124:2503–12.
736 [108] Waterhouse BD, Moises HC, Woodward DJ. Noradrenergic modulation of somatosensory
737 cortical neuronal responses to iontophoretically applied putative transmitters Exp Neurol
738 1980;69:30-49.
739 [109] Waterhouse BD, Moises HC, Woodward DJ. Alpha-receptor-mediated facilitation of
740 somatosensory cortical neuronal responses to excitatory synaptic inputs and iontophoretically
741 applied acetylcholine Neuropharmacol 1981;20:907-20.
742 [110] Devilbiss DM, Waterhouse BD, Berridge CW, Valentino R. Corticotropin-Releasing
743 Factor acting at the Locus Coeruleus disrupts thalamic and cortical Sensory-Evoked Responses
744 Neuropsychopharmacol 2012;37:2020–30.
745 [111] Moore CI. Frequency-dependent processing in the vibrissa sensory system J Neurophysiol
746 2004;91:2390–9.
747 [112] Devilbiss DM, Waterhouse BD. Determination and quantification of pharmacological,
748 physiological, or behavioral manipulations on ensembles of simultaneously recorded neurons in
749 functionally related neural circuits J Neurosci Methods 2002;121:181–98.
750 [113] Poldrack RA, Clark J, Paré-Blagoev EJ, Shohamy D, Creso Moyano J, Myers C, Gluck
751 MA. Interactive memory systems in the human brain Nature 2001;414:546–50.
752 [114] Reber PJ, Squire LR. Parallel brain systems for learning with and without awareness Learn
753 Mem 1994;1:217–29.
754 [115] Yang J, Li P. Brain networks of explicit and implicit learning PLoS ONE 2012;7:e42993
755 doi:101371/journalpone0042993.

[116] Straube T, Korz V, Balschun D, Frey JU. Requirement of β-adrenergic receptor activation and protein synthesis for LTP-reinforcement by novelty in rat dentate gyrus. J Physiol (Lond) 2003;552:953–60.

[117] Tanaka LY, Bechara LRG, dos Santos AM, Jordao CP, de Sousa LGO, Bartholomeu T, Ventura LI, Laurindo FR, Ramires PR. Exercise improves endothelial function: A local analysis of production of nitric oxide and reactive oxygen species Nitric Oxide 2015;45:7–14.

[118] Arnold,WP, Mittal CK, Katsuki S, Murad F. Nitric oxide activates guanylate cyclase and increases guanosine 3':5'-cyclic monophosphate levels in various tissue preparations Proc Natl Acad Sci U S A 1977;74:3203–7.

[119] Hawkins RD, Kandel ER, Siegelbaum SA. Learning to modulate transmitter release: Themes and variations in synaptic plasticity Annu Rev Neurosci 1993;16:625–65.

[120] Hawkins RD, Son H, Arancio O. Nitric oxide as a retrograde messenger during long-term potentiation in hippocampus Prog Brain Res 1998;118:155–72.

[121] Ferris LT, Williams JS, Shen C. The effect of acute exercise on serum brain-derived neurotrophic factor levels and cognitive function Med Sci Sports Exerc 2007;39:728-34.

[122] Goekint M, Heyman E, Roelands B, Njemini R, Bautmans I, Mets T, Meeusen R, No influence of noradrenaline manipulation on acute exercise-induced increase of brain derived neurotrophic factor Med Sci Sports Exerc 2008;40:1990-8.

[123] Griffin ÉW, Mullally S, Foley C, Warmington SA, O'Mara SM, Kelly ÁM. Aerobic exercise improves hippocampal function and increases BDNF in the serum of young adult males Physiol Behav 2011;104:934-41.

[124] Rasmussen P, Brassard P, Adser H, Pedersen MV, Leick L, Hart E, Secher NH, Pedersen BK, Pilegaard H. Evidence for release of brain-derived neurotrophic factor from the brain during exercise Exp Physiol 2009;94:1062-9.

[125] Rojas Vega S, Strüder HK, Vera Wahrmann B, Schmidt A, Bloch W, Hollmann W. Acute BDNF and cortisol response to low intensity exercise and following ramp incremental exercise to exhaustion in humans Brain Res 2006;1121:59-65.

[126] Tang SW, Chu E, Hui T, Helmeste D, Law C. Influence of exercise on serum brain-derived neurotrophic factor concentrations in healthy human subjects Neurosci Lett 2008;431:62-5.

[127] Winter B, Breitenstein C, Mooren FC, Voelker K, Fobker M, Lechtermann A, Krueger K, Fromme A, Korsukewitz C, Floel A, Knecht S. High impact running improves learning Neurobiol Learn Mem 2007;87:597-609.

[128] Berchtold NC, Castello N, Cotman CW. Exercise and time-dependent benefits to learning and memory Neurosci 2010; 167:588-97.

[129] Cotman CW, Berchtold NC. Exercise: a behavioral intervention to enhance brain health and plasticity Trends Neurosci 2002;25:295-301.

[130] Gomez-Pinilla F, Vaynman S, Ying Z. Brain-derived neurotrophic factor functions as a metabotrophin to mediate the effects of exercise on cognition Eur J Neurosci 2008;28:2278-87.

[131] Griesbach GS, Hovda DA, Gomez-Pinilla F. Exercise-induced improvement in cognitive performance after traumatic brain-injury in rats is dependent on BDNF activation Brain Res 2009;1288:105-15.

[132] Huang AM, Jen CJ, Chen HF, Yu L, Kuo YM, Chen HI. Compulsive exercise acutely upregulates rat hippocampal brain-derived neurotrophic factor J Neural Transm 2006;113:803-11.

[133] Liu YF, Chen HI, Wu CL, Kuo YM, Yu L, Huang AM, Wu FS, Chuang JI, Jen CJ. Differential effects of treadmill running and wheel running on spatial or aversive learning and memory: roles of amygdalar brain-derived neurotrophic factor and synaptotagmin 1 J Physiol 2009;587:3221-31.

[134] Yamada K, Nabeshima T. Brain-Derived Neurotrophic Factor/TrkB signaling in memory processes J Pharmacol Sci 2003;91:267–70.

[135] Ji YY, Pang PT, Feng LY, Lu B. Cyclic AMP controls BDNF-induced TrkB phosphorylation and dendritic spine formation in mature hippocampal neurons Nat Neurosci 2005;8:164-72.

[136] Binder DK, Scharfman HE. Brain-derived neurotrophic factor Growth Factors 2004;22:123-31.

[137] Cunha C, Brambilla R, Thomas KL. A simple role for BDNF in learning and memory? Front Mol Neurosci 2010;3:1 doi: 103389/neuro020012010.

[138] Waterhouse EG, Xu B. New insights into the role of brain-derived neurotrophic factor in synaptic plasticity Mol Cell Neursci 2009;42:81-9.

[139] Bailey CH, Kandel1 ER, Harris KM. Structural components of synaptic plasticity and memory consolidation Cold Spring Harb Perspect Biol 2015;7:a021758.

[140] Horvitz JC. Stimulus-response and response-outcome learning mechanisms in the striatum Behav Brain Res 2009;199:129–40.

820 [141] Albouy G, Sterpenich V, Balteau E, Vandewalle G, Desseilles M, Thanh D-V, Darsaud A,
821 Ruby P, Luppi P-H, Degueldre C, Peigneux P, Luxen A, Maquet P. Both the hippocampus and
822 striatum are involved in consolidation of motor sequence memory Neuron 2008;58:261–72.
823 [142] Reznikoff GA, Manaker S, Rhodes CH, Winokur A, Rainbow TC. Localization and
824 quantification of beta-adrenergic receptors in human brain Neurol 1986;36:1067-73.
825 [143] Wickens JR, Horvitz JC, Costa RM, Killcross S. Dopaminergic mechanisms in actions and
826 habits J Neurosci 2007;27:8181–3.
827 [144] Tritsch NX, Sabatini BL. Dopaminergic modulation of synaptic transmission in cortex and
828 striatum Neuron 2012;76:33–50.
829 [145] Chang Y-K, Tsai C-L, Huang C-C, Wang C-C, Chu I-H. Effects of acute resistance
830 exercise on cognition in late middle-aged adults: General or specific cognitive improvement? J
831 SciMed Sport 2014;17:51-5.
832 [146] Hsieh S-S, Chang Y-K, Hung T-M, Fang C-L. The effects of acute resistance exercise on
833 young and older males' working memory Psychol Sport Exerc 2016;22:286-93.
834 [147] Weinberg L, Hasni A, Shinohara M, Duarte A. A single bout of resistance exercise can
835 enhance episodic memory performance Acta Psychol 2014;153:13–9.
836 [148] Judelson DA, Maresh CM, Yamamoto LM, Farrell MJ, Armstrong LE, Kraemer WJ,
837 Volek JS, Spiering BA, Casa DJ, Anderson JM. Effect of hydration state on resistance exercise-
838 induced endocrine markers of anabolism, catabolism, and metabolism J Appl Physiol
839 2008;105:816–24.
840 [149] Tsai C-L, Chen F-C, Pan C-Y, Wang C-H, Huang T-H, Chen T-C. Impact of acute aerobic
841 exercise and cardiorespiratory fitness on visuospatial attention performance and serum BDNF
842 levels Psychoneuroendocrinol 2014;41:121-31.

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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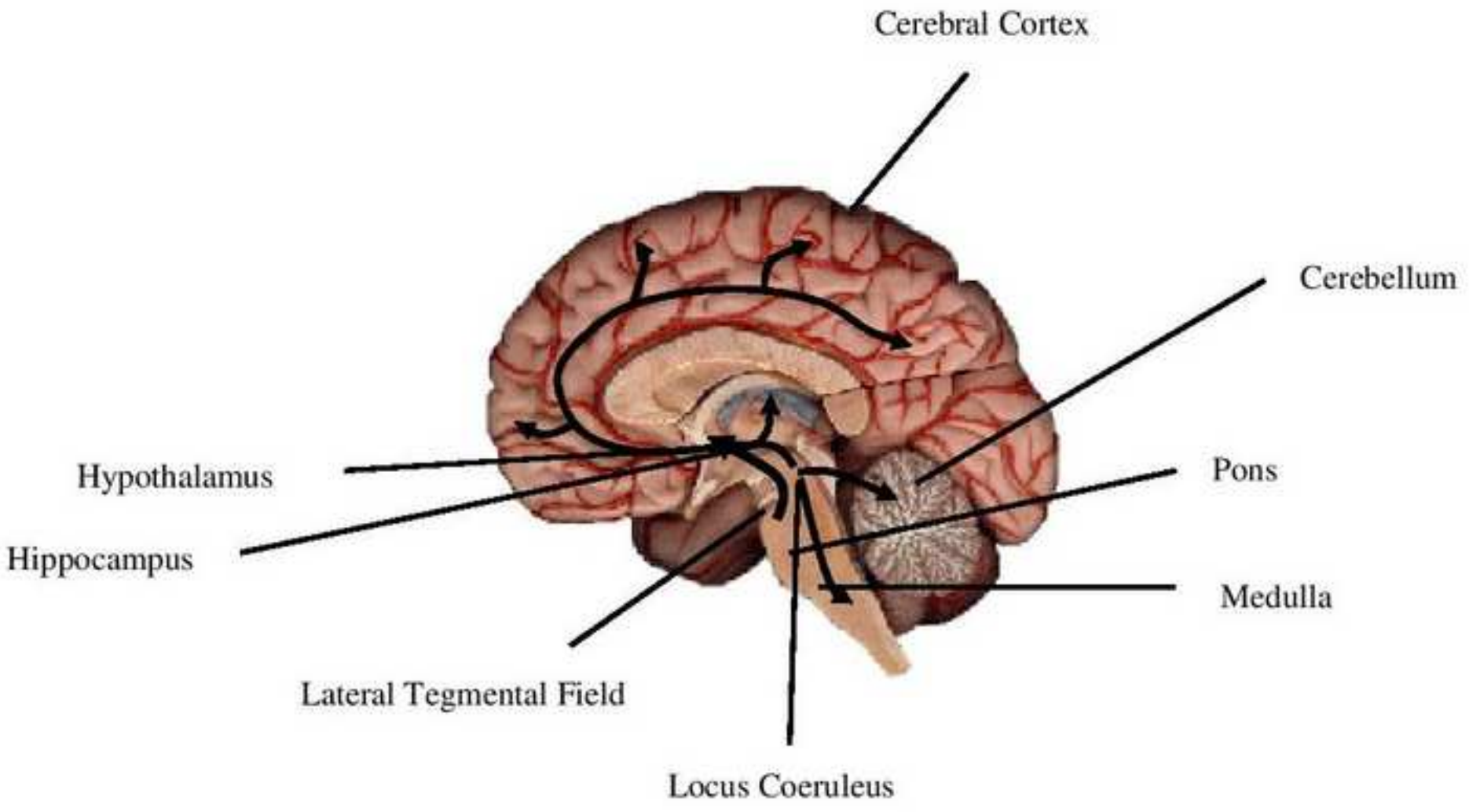

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