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Modulatory effects of physical exercise and transcranial electrical brain stimulation on long-term memory and their associated neural oscillatory activity

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Abstract

By providing a standardised design, this thesis aimed to determine the most effective physical exercise (PE) protocol for long-term memory enhancement, whilst directly comparing it to active rest (AR) and passive rest (PR). Concurrently, EEG was recorded during PE to investigate correlations between neural oscillations and enhanced memory performance. Additionally, some studies demonstrated positive effects of transcranial direct current stimulation (tDCS) on declarative memory. Therefore, the effects of PE and tDCS were compared. Further, this was also the first time that acute PE and tDCS were combined into one intervention to investigate whether their combination would elicit further increases in memory modulation.

In six studies, 181 participants memorised a series of images and were tested using an old/new recognition task. In studies 1-3, effects of different PE protocols and intensities were compared together and with AR and PR. Study 4 compared the effects of tDCS to moderate-intensity PE and PR. Studies 5 and 6 compared the effects of moderate-intensity PE to the combined intervention after retention intervals of 90 min and 24h.

Moderate-intensity PE yielded the greatest enhancements to memory performance compared to PR when tested after 90 min, but not after 24h. While tDCS and PE enhanced memory, the combined intervention impaired memory. Finally, negative correlations between alpha and parietal beta oscillations were correlated to successful memory enhancement, whereas positive correlations between theta, gamma, and frontal beta were correlated with successful memory enhancement. These studies show PE as a potentially successful method of memory enhancement and highlight the complexity of mechanism of action of PE and tDCS in memory enhancement. Together, these findings could have significant implications in the treatment of memory deficiencies. Furthermore, these findings show that tDCS modulates memory similarly to PE, with possible benefits for at-home applications and for people unable to participate in PE.

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Declaration

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Publications:

1. Pyke, W*., **Ifram, F*.**, Coventry, L., Sung, Y., Champion, I., & Javadi, A.-H. (2020). The effects of different protocols of physical exercise and rest on long-term memory. *Neurobiology of Learning and Memory*, *167.*
2. **Ifram, F***., Pyke, W., Turk, S., Amin, M., Osei-Abrokwah, D., & Javadi, A.-H., Combining electrical brain stimulation and physical exercise impairs long-term memory performance. Manuscript in preparation.

* These authors contributed equally.

Conferences:

1. **Ifram, F**., Pyke, W., Osei-Abrokwah, D., & Javadi, A.-H. “Physical exercise and brain stimulation alone enhance long-term memory, but their combination does not” Memory Malleability over Time, University of Kent, Canterbury, UK

2. **Ifram, F**., Pyke, W., Coventry, L., Sung, Y., Champion, I., & Javadi, A.-H. “The effects of different protocols of exercise and rest on memory” Memory Malleability over Time, University of Kent, Canterbury, UK
3. **Ifram, F**., Osei-Abrokwah, D., & Javadi, A-H. “Enhancing long-term memory using physical exercise and electrical brain stimulation” British Association for Cognitive Neuroscience Annual Scientific Meeting, University of Glasgow, UK
4. Javadi, A-H., **Ifram, F**., Boccara, L. “Theta band activity during physical exercise correlates with memory improvement” Experimental Psychology Society, Durham, UK
5. Javadi, A.-H., **Ifram, F**., Champion, I., & Boccara, L. “Neural correlate of memory enhancement during physical exercise” International Conference on Memory (ICOM) Budapest, Hungary.
6. Javadi, A.-H., & **Ifram, F**. “Physical exercise improves long-term memory no less than transcranial direct current stimulation” 6th International Conference on Transcranial Brain Stimulation Göttingen, Germany.

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Chapter 1: Introduction

The studies in this thesis investigated the modulatory effects of physical exercise, wakeful rest, and transcranial electrical brain stimulation on long-term memory. Of particular interest were the effects on the consolidation of long-term memory. Additionally, I was interested in the contribution of the dorsolateral prefrontal cortex (DLPFC) in declarative memory and as such, the left DLPFC was the chosen stimulation site for transcranial direct current stimulation (tDCS). As such, declarative memory was the chosen domain as this enabled equal comparisons between the effects of tDCS and physical exercise on long-term memory. Concurrently, EEG was recorded during physical exercise to investigate the correlations between neural oscillatory activity and enhanced long-term memory performance. These studies were categorised into three chapters. (1) Chapter 2 investigated the effects of physical exercise and wakeful rest. (2) Chapter 3 compared the effects of moderate-intensity physical exercise to transcranial direct current stimulation, and whether a combination of these two interventions would elicit further memory modulation. (3) Chapter 4 examined how oscillatory activity during physical exercise is correlated to long-term memory performance. In this chapter, I provide a review of the current literature relevant to these studies. Figure 1 shows a schematic of the research topics reviewed in this chapter as well as the introduction sections of all the ensuing chapters.

1. Memory

Memories are the faculty of the brain that derive from the innate ability to learn (encode), store (consolidate), and recall (retrieve) information from past experiences. Physiologically, memories are sets of encoded neural connections reconstructed from previous experiences via the synchronous firing of neurons that were involved in the original experience (Mastin, 2019).

Despite everyday forgetting, long-term memories decay very little over time and can store seemingly unlimited information (Bear et al., 2007; Mastin, 2019). Information from the short-term memory store is converted into long-term memories via memory consolidation, where different forms of information are stored using specific memory systems (Coles & Tomporowski, 2008; Javadi & Cheng, 2013; Mastin, 2019). Long-term memory is split into two types of memory domains: explicit (declarative) and implicit (procedural). Declarative memory refers to the memories that can be explicitly stored and consciously recalled, such as facts and events. The declarative memory domain is further divided into two sub-categories: episodic- and semantic memory. Episodic memories are related to personally experienced events reconstructed from retrieval cues, whereas semantic memories represent the memory of facts independent of personal experiences and the spatial and temporal context in which they were acquired (Mastin, 2019; Roediger, 1990; Tulving, 2002; Wheeler & Ploran, 2009).

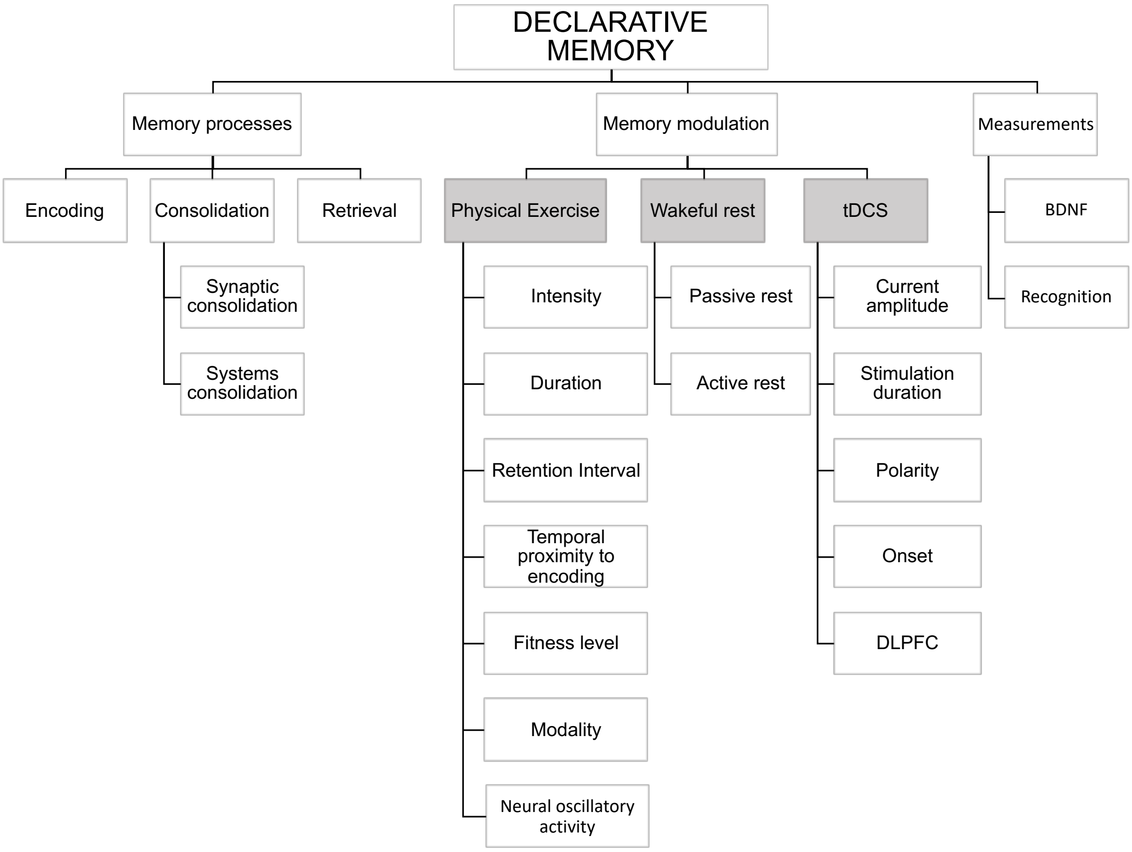
1.1 Declarative memory system

Declarative (explicit) memory is the conscious, intentional recollection of factual information, previous experiences, and concepts (Ullman, 2004). Declarative memory requires learning with presentation of a stimulus and response and can be divided into personal experiences (episodic memory) and factual information (semantic). The cerebral cortex, hippocampus, and parahippocampal region form the components of the declarative memory system. The parahippocampal region is composed of the perirhinal-, parahippocampal-, and entorhinal cortices, which facilitate communication between parts of the cerebral cortex, known as cortical association areas, and the hippocampus (Eichenbaum, 2011; Loprinzi et al., 2017). Because the hippocampus is able to receive input from almost all sensory domains, declarative memory is highly accessible via numerous routes of cortical expression (Loprinzi et al., 2017).

Since information travels from the cortex to the parahippocampal region and then to the hippocampus, hippocampal processing is dependent on several cortical inputs. As reviewed by Loprinzi and colleagues (2017), two forms of information enter the parahippocampal regions from neocortical areas: Pathway A, which denotes representations of new items (e.g., people, objects) enters the lateral part of the entorhinal cortex, and Pathway B, which denotes contextual representations (e.g., Time, location, emotion) enters the medial part of the entorhinal cortex. These pathways then merge in the hippocampus where they are processed. This information is then directed back to the parahippocampal regions and, ultimately, to the cerebral cortex. Essentially, during encoding, the perirhinal cortex processes object representations, the parahippocampal cortex processes contextual representations, and the hippocampus processes the associations between the two cortices (Eichenbaum, 2011; Loprinzi et al., 2017).

Figure 1

Schematic of the research topics reviewed in this thesis.



Note: Greyed boxes denote the interventions used in this thesis.

2. Memory processes

The development of long-term memory consists of three distinct stages: encoding, consolidation and retrieval.

2.1 Encoding

The acquisition of a memory begins with perception and attention, which are regulated by the thalamus and frontal lobe (Mastin, 2019; Sperling, 1967). This experience becomes more likely to be encoded as an engram trace (residing in specific cell assemblies) via increased neuronal firing (Barnes et al., 2005; Dudai, 2004b). This memory trace indicates the formation of a short-term memory, which is then consolidated into a long-term memory (Bear et al., 2007).

Contextual factors occurring during encoding influence memory retrieval. That is, because contextual information is stored alongside memory targets, contextual cues that are present during encoding (e.g. emotional state, location, sounds) will influence memory retrieval if they are also present or absent during recall. The encoding specificity principle (Tulving, 1983) is the general principle which states that memory performance is enhanced when the contextual information present at encoding is also present during the retrieval of the memory.

This type of context-dependent learning has also been exhibited in the physical exercise domain. In a study by Miles and Hardman (1998), participants learned a list of words in two physiological states – exercise and rest – and then recalled said list in a state consistent with encoding or in the alternative state (Miles & Hardman, 1998). In line with the encoding specificity principle, they found that memory performance was optimised when encoding and recall occurred in the same state: memory recall in a resting state was enhanced when encoding also took place in a resting state, and vice versa. The authors suggested that this state-dependent memory should be seen as a specific form of context-dependent memory (Miles & Hardman, 1998).

Other studies have demonstrated that physical exercise, specifically running, generates neural oscillations where the amplitude and frequency of these oscillations are linked to running speed (for review: Loprinzi et al., 2017). Moreover, as a result of acute maximal aerobic physical exercise, a study demonstrated that P300 amplitude and P300 latency increased and decreased, respectively, and suggested that exercise, independent of aerobic fitness, increases general arousal level, known to enhance memory for high-priority information (Magnié et al., 2000).

2.2 Consolidation

Memory consolidation refers to memory phase in which post-acquisition stabilisation of the primary memory trace occurs (Dudai, 2004b). There are two complementary levels of memory consolidation: synaptic consolidation and system consolidation. Together, they form a system where engrams are consolidated and reconsolidated over time (Dudai, 2012).

2.2.1 Synaptic consolidation.

Synaptic consolidation, also known as cellular consolidation, is fast and occurs within minutes (up to a few hours) of encoding (Dudai, 2004b) and involves the fixation of memory (Loprinzi et al., 2017). This type of consolidation occurs in synapses and depends on crosstalk between these synapses and their cell body, hence the name (Dudai, 2004b). Shortly after encoding, short-term memories that undergo synaptic consolidation become resistant to interferences that can prevent their conversion into long-term memories (Dudai, 2004b).

Evidence suggests that some memories may become labile once reactivated and may require further consolidation (reconsolidation) to again become resistant to interference. Yet, it appears that reconsolidation is not required for every reactivation (retrieval) of a memory. Instead, it seems to play a more crucial role when new information becomes available during retrieval (Dudai, 2004b; Loprinzi et al., 2017). This is in line with the understanding memories are recurrently modified throughout a lifetime (Eichenbaum, 2011; Loprinzi et al., 2017).

Neurons encode memory by modifying functional connection strength and involves three stages: electronic conduction, action potential, and synaptic transmission (Loprinzi et al., 2017). Loprinzi and colleagues postulated that while short-term studying (e.g. exam revision) may invoke a weak input, it is not enough to produce potentiation, thereby preventing neurons from encoding what was learned during the short-term studying. Physical exercise, on the other hand, may invoke an input strong enough to produce potentiation. If short-term studying is paired in close temporal proximity to physical exercise, the weak input (learning the memory task) studying can concurrently be potentiated with the stronger input (physical exercise) (Eichenbaum, 2011; Loprinzi et al., 2017). This associativity is in line with several studies showing that physical exercise prior to encoding enhances memory (Frith et al., 2017; Sng et al., 2018). Further, physical exercise is also associated with the upregulation of cAMP-response-element binding protein (CREB). In turn, CREB is linked to exercise-induced upregulation of hippocampal brain-derived neurotrophic factor (BDNF) (Chen & Russo-Neustadt, 2009). Since both CREB and BDNF are associated with enhanced memory and cognition, it is thought that physical exercise primes neuronal cells into encoding a memory (Chen & Russo-Neustadt, 2009; Loprinzi et al., 2017).

The pre-encoding memory-enhancing effect of physical exercise falls in line with one of the main cellular mechanisms underlying learning and memory: long-term potentiation (LTP). LTP has been shown to be dependent on local events, as well as the prior activity of the neuron (Frey & Morris, 1997). As physical exercise facilitates LTP (in animal models; LTP-like in humans), LTP in turn can increase dendritic spine length (Loprinzi et al., 2017). This is important because the structural plasticity of dendritic spines is thought to underlie memory formation (Borczyk et al., 2019).

2.2.2 Systems consolidation

Whilst a lot of research has been done on synaptic consolidation, less is known about systems-level consolidation. Systems consolidation is a slower process that can take weeks, months, or years. It refers to the post-encoding time-dependent reorganisation of brain systems and the rewiring of connections and pathways (Dudai, 2004; McGaugh & Roozendaal, 2009; Payne & Kensinger, 2010; Loprinzi et al., 2017). It is thought that synaptic consolidation mechanisms act as a subroutine to systems consolidation (Dudai, 2012).

Not only does pre-encoding physical exercise show enhanced memory performance, but post-encoding physical exercise (during consolidation) has also been shown to facilitate memory retrieval (Pyke et al., 2020; Segal et al., 2012; Snigdha et al., 2014). Studies have shown that when post-encoding physical exercise is performed in contiguous proximity to encoding (beginning of consolidation), memory performance on an old/new recognition task (Pyke et al., 2020) and free recall task (Kao et al., 2018) is enhanced. Moreover, it has been suggested that the post-encoding exercise-induced enhancements on memory may be related to noradrenergic mechanisms (da Silva de Vargas et al., 2017). Other studies have demonstrated that physical exercise is also able to enhance memory performance when performed a while after encoding (van Dongen et al., 2016).

As previously mentioned, systems consolidation refers to the reorganisation of a memory trace to brain systems. Several studies have shown memories can benefit from a post-encoding period free of retroactive interference (a period free of new learning that may interfere with the newly encoded memory). This typically comes in the form of sleep or wakeful rest (Martini et al., 2017; McDevitt et al., 2014; Mercer, 2015; Stickgold, 2005).

A study by Loprinzi and Loenneke (2015) found that physical exercise helps facilitate optimal sleep duration, which suggests an important role for exercise in memory consolidation (Loprinzi & Loenneke, 2015). Additionally, another study found that high intensity physical exercise increases slow wave sleep and sleep efficiency, supporting the hypothesis of sleep-dependent memory processing (Dworak et al., 2008).

2.3 Retrieval

Retrieving a memory involves the re-accessing of information from a previously encoded memory trace. Memory retrieval requires retrieval cues to engage the circuit and replay the specific nerve pathways generated during the encoding of the original memory (Dudai, 2004a; Loprinzi et al., 2017). The speed at which retrieval occurs is dependent on the strength of these pathways (Bear et al., 2007; Jafarpour et al., 2014; Mastin, 2019; Tsien, 2007). This replay directs the memory from the long-term memory store to short-term memory access where it becomes accessible. After the memory is accessed, it can be reconsolidated and returned back to the long-term memory store, further strengthening the pathway (Javadi & Cheng, 2013).

In Dudai's book (2004), he describes two main retrieval components: item-specific and item-invariant. The item-specific component promotes recovery of the particular memory item, whereas the item-invariant component searches for items in memory, as well as allocates mental resources, controls the process, and verifies the outcome (Dudai, 2004a; Loprinzi et al., 2017).

Linking physical exercise with cue-based memory retrieval has proven to be rather challenging, however, Loprinzi and colleagues (2017) speculated that it may be possible for pre-retrieval physical exercise to enhance the item-invariant component of cue retrieval by facilitating the allocation of mental resources (Loprinzi et al., 2017).

3. Memory modulation

Although the brain is able to retain an immeasurable number of memories, not all of these memories are as memorable as others. Some experiences may be remembered for a lifetime, whilst others for a few days or minutes, and some, not at all. Research on the modulation of memory investigates the neurobiological processes and systems that contribute to the differences in memory strength (Roozendaal & McGaugh, 2011).

Researchers have shown several systems capable of modulating memory, including internal systems such as adrenal stress hormones (Roozendaal & McGaugh, 2011), and BDNF (Bekinschtein et al., 2014), and external systems such as sleep (Diekelmann & Born, 2010; Gais et al., 2006), wakeful rest (Craig, Dewar, Della Sala, & Wolbers, 2015; Kuschpel et al., 2015), transcranial electrical stimulation (Javadi & Walsh, 2012), physical exercise (Pyke et al., 2020; Tomporowski, 2003) and pharmacological interventions (Cahill & Alkire, 2003; Stimpson et al., 2018). This thesis investigates three external modulatory systems: physical exercise, wakeful rest, and transcranial direct current stimulation (tDCS) with a particular focus on effects of physical exercise on memory.

3.1 Physical exercise

Due to advancements in medicine and medical technologies, global life expectancy has been substantially increasing and is expected to continue to rise. Therefore, the enhancement of neurocognitive functions is becoming considerably more important for the general public as subclinical neurocognitive deficits are linked to cognitive impairment and neurodegenerative diseases, including Alzheimer's disease. One of these strategies to enhance cognitive function that is gaining traction in academic research is the use of physical exercise.

Research has shown positive effects of physical exercise on the maintenance, and even enhancement, of cognitive functions (Roig et al., 2013), with the general consensus being that physical exercise is optimally effective for enhancement of processes occurring for executive control that involve the frontal areas of the brain (Colcombe & Kramer, 2003; Roig et al., 2013). Many of the early studies have used physical exercise to assess its effects on attention (Cerrillo-Urbina et al., 2015), speed processing (Tam, 2013), or decision-making (Davranche et al., 2006). However, because physical exercise brings with it a long list of associated physiological changes – many of which are maintained beyond the period of exercise – investigational research into its effects on higher cognitive functions and memory is becoming more important and accordingly, rapidly growing (Tomporowski, 2003).

Physical exercise studies typically employ either acute or long-term interventions. Acute interventions consist of a single bout of physical exercise, whereas long-term interventions consist of several bouts performed at different timepoints within the space of weeks or months (Roig et al., 2013). The number of studies investigating the effects of chronic physical exercise on executive functions, especially working memory, are relatively low, with results being quite ambiguous (for review: Xue et al., 2019). The relationship between chronic physical exercise and executive functions and/or memory can be moderated by several factors, including task-related factors (e.g. exercise intensity or duration), individual factors (e.g. age, gender, fitness level) and contextual factors (e.g. study setting) (Xue et al., 2019). Furthermore, the effects of long-term physical exercise likely depend on the cumulative effects that acute bouts of physical exercise have on the brain areas responsible for memory processing as a whole (Roig et al., 2013). However, this thesis focuses solely on acute physical exercise interventions.

The benefits of acute physical exercise on physical wellbeing are well-documented (Penedo & Dahn, 2005). A continuously growing body of literature shows that acute physical exercise is also positively associated to certain aspects of cognition, particularly in tasks involving the activation of frontal areas of the brain (e.g. memory) (Roig et al., 2013). Several studies have demonstrated enhancing effects of acute physical exercise on long-term memory. For example, Winter and colleagues (2007) found that acute bouts of physical exercise enhanced long-term word recall. Additionally, Segal and colleagues (2012), found that a short bout of physical exercise was enough to enhance image recall in healthy participants as well as patients with mild cognitive impairment.

Whilst many studies have demonstrated a supporting role of acute physical exercise as a positive memory modulator (Hötting et al., 2012), other studies have shown no effect (Madden et al., 1989), or even detrimental effects (Pontifex et al., 2016). Similarly, review papers and meta-analyses have also debated the magnitude of exercise-induced improvements in cognitive function (Smith et al., 2010). These inconsistent results may be attributed to several factors: (a) exercise intensity, (b) exercise duration (Labban & Etnier, 2011a), (c) exercise modality (d) exercise onset relative to encoding (before, during, or after) (Roig et al., 2013), (e) participant fitness level (Colcombe & Kramer, 2003), and others (Etnier et al., 1997; Potter & Keeling, 2005; Winter et al., 2007). Table 1 summarises the outcomes of some of these studies.

Table 1.

Summary of exercise studies describing their intervention duration, intensity and onset, the memory task used, and outcome.

Authors	N	Intervention	Memory task	Outcome
Madden et al., 1989	85	Cycle ergometer. 70% HRmax for 30 min.	Reaction time test	No performance difference between exercise group and non-exercise group.
Arcelin., et al. 1997	22	Cycle ergometer. 60% Pmax	Visual choice reaction task	Significant interaction effect between cognitive task and exercise duration for mean RT values. Improved cognitive performance during PE.
Brisswalter et al., 1997	20	Cycle ergometer. 20 – 80% Pmax	Choice reaction test	Improvement in cognitive performance from 40% Pmax
Chmura et al., 1998	17	Cycle ergometer. >10% anaerobic threshold based on blood lactate levels.	Choice reaction test	Deterioration of cognitive performance.
Arent & Landers, 2003	104	Cycle ergometer. Participants assigned to one of eight arousal groups (between 20 - 90% heart rate reserve)	Simple response time task	Optimal performance seen at 60 – 70% of maximum arousal, as predicted by inverted-U hypothesis.
Chang & Etnier, 2009	68	40%, 70%, or 100% of 10-repetition maximal resistance exercise	Stroop Test. Paced Auditory Serial Addition Task.	There is a significant linear effect of exercise intensity on information processing speed, and a significant quadratic trend for exercise intensity on executive function. Moderate intensity exercise is most beneficial for

				executive function, whereas high intensity exercise benefits speed of processing.
Labban et al., 2011	48	Cycle ergometer. 20 min moderate-intensity	Paragraph recall. Participants had to recall as much information after listening to two paragraphs	Pre-encoding exercise enhanced memory performance.
Salas et al., 2012	80	Brisk 10 min walk	Word-list memory task	Students who walked before encoding had significantly higher recall compared to control (sitting)
Basso et al., 2015	85	Cycle ergometer. High intensity for 50 min	Hopkins verbal learning test revised, modified Benton visual retention test, Digit span	Exercise improved prefrontal-cortex-dependent memory function.
Loprinzi et al., 2015	4386	Low, moderate, and high intensity free-living physical activity	Spatial span and paired associates	Concentration-related cognition was significantly higher after a 30-min acute bout of moderate-intensity exercise compared with cognitive assessment without exercise.
Hötting et al., 2016	81	Cycle ergometer. Low and High intensity for 30 min	Auditory stimuli	Exercise after learning did not enhance the absolute number of recalled words. However, less words were forgotten after 24 hr by participants in the high-intensity group.

Pontifex et al., 2016	21	Cycle ergometer. Submaximal intensity at 60% Pmax for 10 min	Paired associates memory task	Exercise 1 – 2 hr post encoding was detrimental to the maintenance of information in long-term memory. Exercise 1 hr prior to memory retrieval was associated with superior memory performance.
Van Dongen et al., 2016	72	Cycle ergometer. 35 min intermittent high-intensity.	Paired associates learning task	Exercising 4 hr after encoding enhanced memory.
Crush & Loprinzi 2017	352	Treadmill. Total of 16 groups ranging from 10 – 60 min exercise with different durations of recovery period ranging from 5 – 30 min.	Spatial span	Shorter recovery period was beneficial for memory.
Frith et al., 2017	88	15-min bout of progressive maximal exertion treadmill exercise	RAVLT	High-intensity exercise prior to memory encoding (vs. exercise during memory encoding or consolidation) was effective in enhancing long-term memory
Most et al., 2017	82	5 min of step-exercise	Paired faces and names	5 min of low impact exercise immediately after encoding showed better recall for paired associations.
Sng et al., 2017	88	Brisk 15 min walk at moderate intensity	RAVLT	Walking before encoding was effective in influencing long-term episodic memory.
Delancey et al., 2018	40	Treadmill. 15 min high-intensity	RAVLT	High-intensity exercise during consolidation increased memory function.

Wade et al., 2018	34	Treadmill. 15 min at self-selected brisk walking pace	Emotional memory assessment	No significant differences.
Zuniga et al., 2019	30	Treadmill. 10 min at light or moderate intensity briss walking	Free recall, judgements of learning, metacognitive accuracy	Light intensity and moderate intensity brisk walking on a treadmill recalled more words than control. Similar results were observed for “high-fit” to “low-fit” participants.

Notes: Pmax: power associated with maximal oxygen uptake. RAVLT: Rey Auditory Verbal Learning Test

This section will highlight the mechanism of effects for the aforementioned factors specific to acute physical exercise.

With regards to the effects of physical exercise on the declarative memory system, animal models have shown that exercise increases hippocampal neurogenesis as well as learning and reduces age-related decreases in neuronal populations (Erickson et al., 2011). This process is thought to be somewhat facilitated by the astrocyte-neuron lactate shuttle (ANLS). First presented by Magistretti and Pellerin (1996), the ANLS hypothesis states that in response to increases neuronal activity, astrocytes increase their rate of glycolysis and, consequently, the release of astrocytic lactate into the extracellular space (Magistretti & Pellerin, 1996). This is important because the released astrocytic lactate is taken up as an energy substrate by neurons that are contingent on this during synaptic transmission to (a) generate action potentials and (b) for neuronal transmission (Loprinzi et al., 2017; Magistretti & Pellerin, 1996; Mason, 2017). Linking this back to exercise, studies have shown that exercise upregulates astrocytic lactate transporter levels, and therefore, increases the efficacy of the ANLS (Overgaard et al., 2012).

Furthermore, animal models have also shown that physical exercise is linked to increased dendritic spine density in the CA1 pyramidal neurons and the entorhinal cortex (Loprinzi et al., 2017). Dendritic spines are membranous organelles where the majority of excitatory synaptic signalling takes place and provide an anatomical substrate for memory storage (Alvarez & Sabatini, 2007). One animal study linked decreased spine density with reduced hippocampal learning and memory (Von Bohlen Und Halbach et al., 2006). Other studies have found decreased dendritic spine density in neurodegenerative diseases, especially Alzheimer’s disease, in which the greatest correlate of cognitive dysfunction is believed to be the loss of synapses (Bhatt et al., 2009). Therefore, increased spine density in the CA1 pyramidal neurons and the entorhinal cortex is significant because the pathways by which the parahippocampal area (where the entorhinal cortex is located) projects into the hippocampus go through the CA1 pyramidal cells. Finally, physical exercise has also been shown to increase BDNF expression in the perirhinal cortex, which is commonly associated with enhanced episodic, recognition, and verbal memory (for review: Szuhany, Bugatti, & Otto, 2015).

3.1.1 Exercise intensity.

To further understand the mechanisms by which physical exercise modulates memory, several studies have investigated the effects of intensity, where a potential dose-response relationship between intensity and memory has been observed. Some of these studies have found an inverted-U relationship, or a linear relationship, whilst others have not found a dose-response relationship (for review: Chang & Etnier, 2009).

Before discussing the effects of exercise intensity on memory, it is important to touch on how exercise intensity boundaries are identified. When physical exercise is standardised according to an absolute external workload, it may lead to large variations in internal cardiovascular and metabolic stress between individuals (Mann et al., 2013). As such, relative intensity is usually prescribed as it aims to account for physiological differences to produce approximated equivalents of exercise stress among individuals (Mann et al., 2013). In studies employing physical exercise, this has typically been done by using $\%VO_{2max}$ or $\%HR_{max}$. Whilst these are the preferred methods to define exercise intensity by many studies (Dworak et al., 2008; Hötting, Schickert, Kaiser, Röder, Schmidt-Kassow, et al., 2016b; Lambourne, 2012; Olson et al., 2016), some have argued against them and instead suggest prescribing exercise relative to an individual's oxygen consumption reserve (VO_2R; VO_{2max}

minus the resting oxygen consumption (VO_2)) because VO_{2max} does not consider individual differences in resting metabolic rate (Mann et al., 2013; Swain & Leutholtz, 1997). Unlike the use of VO_{2max} or HR_{max}, the use of %VO_2R has been shown to place individuals at equal intensity above resting levels (for review: Mann et al., 2013). In support of this claim, some studies report that some individuals may be above or below metabolic thresholds at the same %VO_{2max} or %HR_{max} (Azevedo et al., 2011). However, the use of threshold-related exercise prescription does come with certain detriments compared to the use of the more traditional %VO_{2max} or %HR_{max}. Threshold measurements have been shown to have larger day-to-day variations than %VO_{2max} or %HR_{max} and cannot be considered accurate without verification trials. Verification trials are laborious and require blood lactate sampling, which some participants may find aversive (Mann et al., 2013).

Although not as widely used, salivary cortisol is another method that aims to confirm exercise intensity. McGuigan and colleagues demonstrated that salivary cortisol responses are significantly different immediately following exercise between low and high intensity exercise sessions and that salivary measures of cortisol can be used to delineate between these two exercise bouts (McGuigan et al., 2004).

For Studies 1 – 6, I took the traditional approach and used %HRmax. In addition to this, I used the Rating of Perceived Exertion (RPE) scale (6 – 20) developed by Borg (1982) as a post-hoc analysis to confirm the prescribed intensity boundaries. Using the RPE scale improves safety and reliability of the test when used with objective measures such as HRmax (Muotri et al., 2017), and correlates well with physiological measures of stress and arousal and psychological measures of exhaustion (Borg, 1985; Muotri et al., 2017). Initially, I had also taken salivary samples at three timepoints (before exercise, immediately after exercise, and after memory task), however, due to freezer failure (where samples were stored) this confirmatory method had to be disregarded.

Humphreys and Revelle (1984) suggested the dose-response relationship between arousal and cognitive performance is specifically linked to the type of cognitive task (Humphreys & Revelle, 1984). In line with this, a study by Arent and Landers (2003) found an inverted-U relationship between physical exercise intensity and memory performance for tasks requiring central processing (higher cognitive functions), and a linear relationship for tasks engaging motor or peripheral processes (Arent & Landers, 2003).

On the basis of the inverted-U relationship, physical exercise performed at a moderate intensity should produce the largest gains on cognitive performance. However, the inverted-U relationship between exercise intensity and memory performance is in contrast to the linear relationship for brain-derived neurotrophic factor (BDNF), a protein strongly associated with learning and memory. Several studies that have investigated the effects of acute physical exercise on the levels of BDNF have shown that high-intensity interventions result in larger increases in circulating BDNF than lower-intensity interventions (Chang et al., 2012; Knaepen et al., 2010). Therefore, because of its links to learning and memory, and assuming that the level of circulating BDNF is an indicator of enhanced cognitive performance, this suggests a linear dose-response relationship between physical exercise intensity and memory performance (*Figure 2*).

Empirical studies investigating the effects of physical exercise on memory generally focus on two intensities: submaximal- and maximal intensity. Submaximal intensity refers to a moderate level of physical exertion, typically within 64-76% of maximum heart rate (HR_{max}), whereas maximal intensity refers to physical exertion that leads to exhaustion (> 90% HR_{max}) (Garber et al., 2011; Pescatello et al., 2014). In a study by Chang and Etnier

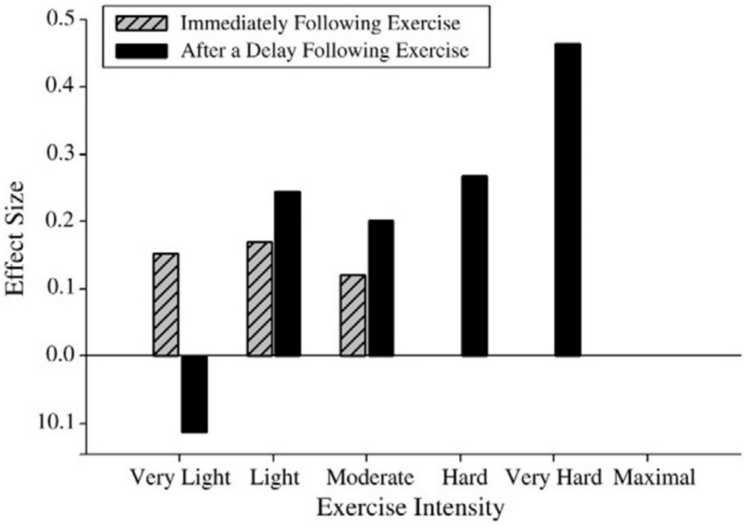
(2009), different intensities of physical exercise were compared. The authors found a significant linear relationship between physical exercise intensity and information processing speed, and a significant quadratic trend for physical exercise intensity on executive function (Chang & Etnier, 2009). Chang and Etnier suggested a dose-response relationship between physical exercise intensity and cognitive performance such that when physical exercise is performed at higher intensities, it benefits processing speed, but when performed at moderate intensities, it benefits executive function (Chang & Etnier, 2009). Likewise, Segal and colleagues (2012) showed that post-encoding submaximal intensity physical exercise is able to enhance memory consolidation (Segal et al., 2012).

Coles & Tomporowski (2008) demonstrated that submaximal intensity physical exercise can change certain aspects of delayed long-term memory (Coles & Tomporowski, 2008). The authors found that the free recall of items in the primacy and recency portions of the word list was maintained following a bout of submaximal intensity exercise but was impaired after rest or non-exercise conditions (participants sat on an exercise bike and performed all experimental procedure without exercising) (Coles & Tomporowski, 2008).

In another study, Hötting and colleagues (2016) compared the effects of submaximal (low intensity <57%) and maximal intensity (>80%) exercise interventions on memory performance. They found that, although neither low or high physical exercise intensities showed any enhancements in memory consolidation when tested 1h after learning, the maximal intensity exercise group forgot less words than control when tested 24h after learning (Hötting, Schickert, Kaiser, Röder, Schmidt-Kassow, et al., 2016). Whilst these results do not show enhanced memory performance, they demonstrate a linear relationship between physical exercise intensity and memory retention. Additionally, this linear relationship matches the mean serum BDNF levels after each physical exercise intervention, where higher serum BDNF predicted better memory retention (*Figures 3* and *4*).

Figure 2.

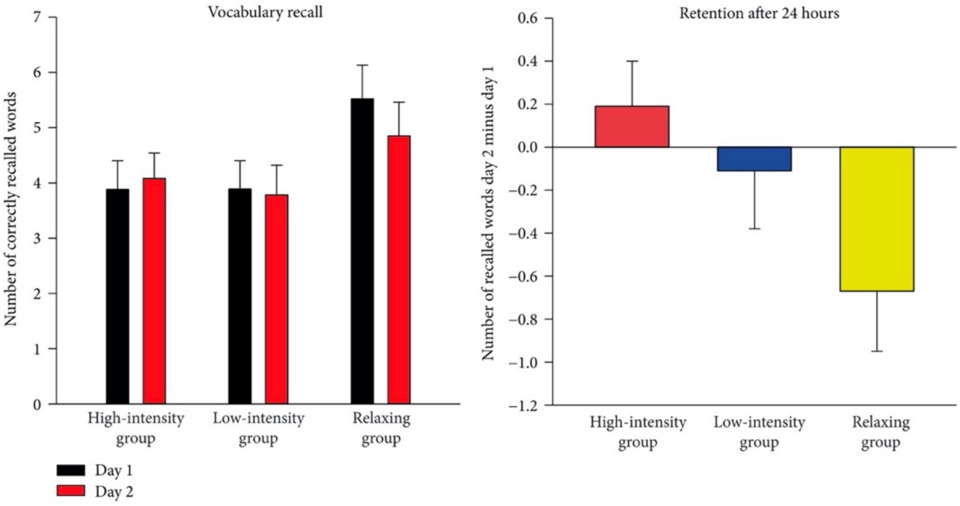
Effect size as a function of paradigm and exercise intensity.



Note: Taken from Chang et al. (2012)

Figure 3.

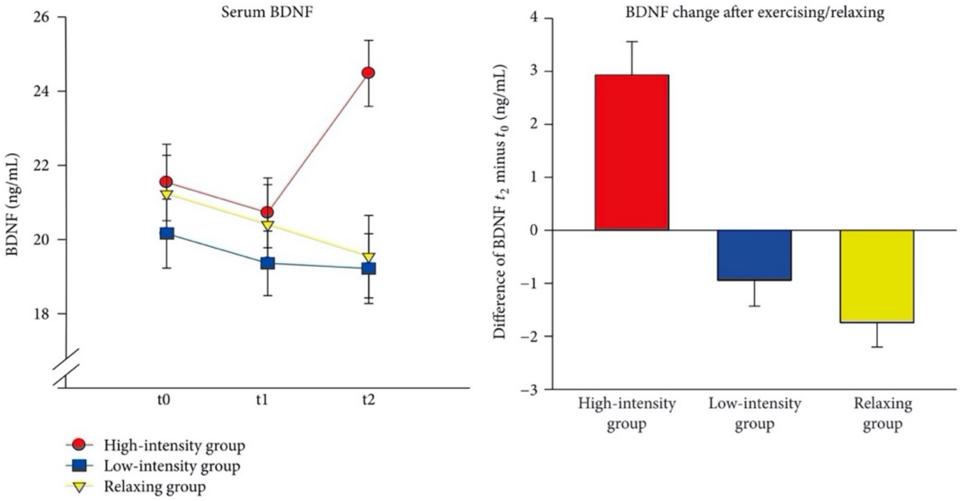
Memory performance for newly learned vocabulary.



Note: (a) Mean number of correctly recalled words at Day 1 (60 mins) and day 2 (24 hr). (b) Difference in retention after 24 hr. Taken from Hötting et al. (2016).

Figure 4.

BDNF levels



Note: (a) Mean serum BDNF levels at baseline (t0), after learning (t1), and after exercising/relaxing (t2). (b) Mean changes in serum BDNF from baseline to assessment after exercising/relaxing. Taken from Hötting et al., (2016).

3.1.2. Exercise duration.

The effects of exercise duration on memory have not been thoroughly investigated. A meta-analytic review by Petruzzello and colleagues (1991) found that acute physical exercise lasting a minimum of 20 min and up to 1h can reduce state and trait anxiety (Petruzzello et al., 1991). However, periods that go beyond the hour mark (considering participant fitness level) tend to lead to symptoms of fatigue, such as dehydration and hypoglycaemia (Brisswalter et al., 2002; Petruzzello et al., 1991). This falls in line with the inverted-U hypothesis, which would predict it diminishing cognition with increasing physical exercise durations.

Brisswalter and colleagues (2002) highlighted that the lack of studies available on the effects of physical exercise duration on memory are to blame for the inconsistent meta-analyses. For example, findings from the meta-analysis by Etnier and colleagues (1997) found no link between exercise duration and memory performance. However, in another meta-analytic review from the same year by Arcelin and colleagues, findings indicate a significant interaction effect between cognitive task and exercise duration (Arcelin et al., 1997).

As mentioned in the exercise intensity section (3.1.1), Labban and Etnier (2011) suggest that post-encoding physical exercise does not enhance long-term memory performance, whereas the study by Segal and colleagues (2012) found enhancing effects. Upon closer examination of their interventions, significant differences in exercise duration are evident. Furthermore, differences in the duration of the retention interval (i.e. the period between the end of exercise intervention and the beginning of the memory task) are also noted. Specifically, in the study by Segal and colleagues (2012), the physical exercise intervention lasted 6 min and recall was tested 1 hr after, whereas the study by Labban and Etnier (2011) employed an exercise intervention that lasted 30 min and recall was tested immediately after. Not only does this highlight a role for the duration of physical exercise on long-term memory performance, but it also highlights a role for the duration of the retention interval.

3.1.3 Retention interval.

The importance of the retention interval was further investigated in a study by Hötting and colleagues (2016). Results indicated that memory recall was not enhanced when tested immediately after the physical exercise intervention (Hötting et al., 2016). Instead, it was shown that less words were forgotten on the recall task when tested 24h after exercise. This is in line with other studies showing enhanced memory performance after longer retention interval periods (Roig et al., 2012). Roig and colleagues (2012) suggested these findings may indicate that memory tests administered too soon after learning are disrupting the memory traces from undergoing proper consolidation to become resistant to interference (Hötting et al., 2016; Roig et al., 2012). Moreover, in their meta-analytic review, Roig and colleagues (2013) found that memory retention was enhanced when tested after a delay of 1 and 7 days post-encoding, but not when memory was tested shortly after encoding (Roig et al., 2013).

3.1.4 Temporal proximity of exercise relative to encoding.

The physical exercise-memory relationship is complex and intertwined with many variables. The timing of exercise relative to encoding is another key modulator of the effects of physical exercise on memory. Whilst some studies have investigated the effects of physical exercise duration or intensity on memory, far fewer studies have investigated the effect of the timepoint at which the physical exercise intervention is performed in relation to the exposure of the information to be remembered (Roig et al., 2016).

Roig and colleagues (2016) argued that the effects of acute physical exercise on long-term memory are time-dependent and that different phases of memory formation are facilitated depending on whether the physical exercise bout is performed before or after encoding (Roig et al., 2016). There is a general consensus that the positive effects of acute physical exercise on memory are maximised when the exercise intervention is performed in close temporal proximity to encoding. This is also supported in animal studies performed on rats, where it is demonstrated that physical exercise can modulate the memory formation process. Siette and colleagues (2014) found that the effects of a single bout of voluntary physical exercise on contextual fear memory are optimised when the exercise intervention is performed with increasingly close temporal proximity to encoding (Siette et al., 2014). Furthermore, they found that when the physical exercise intervention is performed 6h after encoding (temporally uncoupled to encoding), the positive effects of physical exercise are significantly diminished.

Several human studies also support the hypothesis of a time-dependent relationship. Thomas and colleagues (2016) tested the effects of physical exercise on motor memory consolidation when performed immediately, 1h, or 2h after encoding and found significant enhancements only in the group that performed the exercise intervention immediately after encoding (Roig et al., 2016; Thomas et al., 2016). Similarly, another study found that physical exercise performed immediately before encoding facilitates motor skill acquisition, whereas when performed 1h before encoding, no significant enhancements were observed (Statton et al., 2015).

Together, these studies support the hypothesis that when an acute bout of physical exercise is temporally coupled to encoding (specifically before or after), the positive effects on memory are optimised.

3.1.5 Physical fitness.

Many of the studies investigating physical fitness as a modulator of memory have done so by employing cognitive tasks during physical exercise rather than after the exercise intervention. However, more recently, a few studies employed post-exercise recognition tasks to investigate the effects of physical fitness on memory performance.

The difficulty in controlling for participants' physical fitness is one of the variables often linked with explaining the diversity of results (Brisswalter et al., 2002). However, many early studies have suggested a positive relationship between fitness level and cognitive function, particularly mental performance (Sjoberg, 1980). Weingarten and Alexander (1970) found that participants who were physically fit ($MVO_2 > 51\%$) performed better than less fit ($MVO_2 < 51\%$) participants on the Ravens Progressive Matrices (a reasoning ability test) (Weingarten & Alexander, 1970). Another study (Stockfeldt, 1973) showed that during physical exercise the physically fit participants outperformed the less fit participants on a working memory task at almost all workload levels. Furthermore, performance on a difficult motor skill task, presented both before and after physical exercise, was significantly lower for normally fit participants in comparison to extremely fit participants (Hammerton & Tickner, 1968). Finally, a review by Tomporowski and Ellis found that performance on cognitive tasks are generally better performed by physically-fit individuals than less-fit individuals (as assessed by measure of maximal strength, aerobic capacity, or motor fitness index) (Tomporowski & Ellis, 1986). Whilst these results are in favour of increased physical fitness for enhanced cognition, several studies have found no effect of fitness level, and others a detrimental effect on cognition (for review: Sjoberg, 1980).

Inconsistencies in these early studies may be attributed to several factors, such as a discrepancy in what constitutes a "physically fit" participant, but more importantly, the biochemical reactions that take place during physical exercise and the faster physiological recovery of more fit participants. For example, even though physical workloads were matched between the physically "unfit" participants (VO_2 max = 2 – 3.6 litres O_2/min) and the physically "fit" participants (VO_2 max = 3.9 – 5.9 litres O_2/min) to make subjective effort equal, the physical "unfit" group was not able to cope with the accumulation of the by-products that can negatively affect cognition (e.g. carbon dioxide and lactic acid) as well as the physically fit group (Sjoberg, 1980). Furthermore, the physically fit participants showed a faster physiological recovery rate, which results in a lower arousal level that can be especially beneficial to complex working memory tasks (Sjoberg, 1980). Some studies (Castellano & White, 2008; Schulz et al., 2004) have shown that physical fitness level can modulate the BDNF response (a potential mediator; more in section 3.4) to acute physical exercise, thereby also potentially modulating memory performance (for review: Chang et al., 2012). In support of the aforementioned studies, Whiteman and colleagues (2014) showed that physical fitness (assessed by VO_2 max), and BDNF are positively associated with one another and likely predict recognition memory accuracy (Whiteman et al., 2014). Additionally, results from a study by Åberg and colleagues (2009) demonstrated a positive association between cardiovascular fitness and cognitive performance (Åberg et al., 2009).

As mentioned at the beginning of this section, many of the studies investigating physical fitness effects on memory performance have done so by employing cognitive tasks during physical exercise. Whilst the results of these studies provide valuable insight into modulating memory, specifically working memory, they do not provide insight into how declarative memory is affected. This is due to the different mechanisms involved for the different types of memory. This is evident from a review by Chang and colleagues (2012) who report diminished performance from less fit participants when the cognitive task is performed during physical exercise, and positive effects from physically fit participants. Adding to the Sjoberg's suggestions (1980; mentioned above), Chang and colleagues (2012) suggest that, given the limited and constant metabolic capacity of the brain, the neural resources required to perform the physical exercise task compete with the same neural resources required to perform the cognitive task. The authors suggested that this implies that participants with lower physical fitness require more neural resources relative to the physically fit participants as they would require more resources when performing the exercise task, and consequently, have fewer resources available for cognitive performance (Chang et al., 2012). However, this is not the case when assessing physical fitness effects on declarative memory, as such cognitive tasks are not typically assessed during the exercise intervention. This is made evident from the results when cognitive performance is tested after exercise: positive cognitive effects were reported across all fitness levels (Chang et al., 2012).

3.1.6 Exercise modality.

It has previously been shown (Chang et al., 2012) that the neural resources required to perform a physical exercise task compete with the same resources required to perform and cognitive task. Therefore, not surprisingly, the type of physical exercise intervention employed in a study to test memory performance has been suggested to affect behavioural outcomes. Researchers have discussed the role of dual-task demands on attentional allocation during acute physical exercise (Lambourne & Tomporowski, 2010).

In a meta-regression analysis, Lambourne and Tomporowski (2010) found clear differences in cognitive performance when participants completed a cognitive task during cycling or running. Treadmill running, relative to cycle ergometer riding, requires significantly more balance as well as more upper- and lower-body coordination, which indicates a higher likelihood of disruptions in attention when losing balance as this may lead to falling (Lambourne & Tomporowski, 2010). In contrast, however, some studies have shown that different exercise modalities produce similar offline effects on memory and suggest that exercise-induced enhancements to memory consolidation depend primarily on the physiological stimulus rather than the type of exercise (Thomas et al., 2017).

In addition to such comparisons, it is important to iterate some of the differences between continuous training (e.g. cycling continuously for 30 mins) and interval training (e.g. HIIT) and their effects on declarative memory. There is a notable lack of empirical studies aimed at directly comparing the effects of HIIT and continuous moderate-intensity physical exercise on declarative memory, however, many studies have demonstrated the positive effects of continuous moderate-intensity physical exercise on declarative memory (Coles & Tomporowski, 2008; Labban & Etnier, 2011; Pesce et al., 2009). Additionally, more recently, a meta-analysis (Chang et al., 2012) revealed that acute physical exercise performed at higher intensities may facilitate the effects on memory performance more so than continuous moderate-intensity exercise (Kao et al., 2018). Additionally, more and more studies are starting to show that high-intensity interval training (HIIT) may be a suitable alternative to a continuous high-intensity protocol that requires a constant effort to maintain an RPE above a specific level (Kao et al., 2018). HIIT typically involves repeated bouts of short duration, high-intensity exercise followed by either a recovery period or low-intensity exercise. Whilst there is a lack of empirical studies directly comparing the effects of HIIT and continuous moderate-intensity physical exercise on declarative memory, some assumptions can be drawn from research investigating the role of exercise intensity (Section 3.1.1). For example, Hötting and colleagues found that a single bout of HIIT significantly enhanced memory retention after 24h compared to a lighter intensity interval training (Hötting et al., 2016). However, because no direct comparisons between HIIT and continuous moderate-intensity exercise were made, one cannot assume that they would differentially affect declarative memory performance. HIIT and continuous moderate-intensity exercise have been shown to differentially affect task-related brain function, specifically, the P3, an event-related potential (ERP) component commonly elicited in the process of decision making, such as in an oddball paradigm (Kao et al., 2018). Whilst continuous moderate intensity exercise has been shown to increase P3 amplitude (Hillman et al., 2003; Pontifex et al., 2013), and in some cases P3 latency, HIIT, on the other hand, has been shown to decrease P3 amplitude and increase latency compared to rest and continuous moderate-intensity exercise (Kao et al., 2017). Kao and colleagues propose that these changes in P3 amplitude and latency may suggest that interval and continuous training result in different patterns of attentional resource allocation and that this may reflect a cognitive operation that is characterised by enhanced efficiency (Kao et al., 2018). Alternatively, Dempsey and colleagues propose that decreased P3 amplitude as a result of HIIT may be unrelated to task performance, but instead, may be a result of the debilitating effect of exercise-induced fatigue (Dempsey et al., 2006). It is important to note, however, that because exercise duration is a mediator of the effects of physical exercise on declarative memory, the findings from Kao and colleagues may have been confounded by the different physical exercise durations for HIIT (9 min) and continuous moderate-intensity exercise (20 min) protocols (Kao et al., 2017). In a later study, Kao and colleagues compared interval and continuous training using duration-matched physical exercise protocols (Kao et al., 2018) and found that for both protocols a greater number of words were recalled compared to rest. Both protocols led to shorter RT during the flanker task (faster P3 latency) and HIIT resulted in a decreased RT interference score compared to rest. These results are in line with the aforementioned studies that showed increased P3 amplitude for continuous moderate-intensity exercise compared to HIIT and decreased P3 latency for HIIT, suggesting that both protocols may have similar and differential effects on declarative memory (Kao et al., 2018). However, a difference in memory retention (number of correctly recalled words) between the two protocols was not observed, and it was suggested that this may be due to the retention interval duration, where larger facilitation of memory retention is typically seen after longer periods (e.g. 24h) of memory consolidation following high-intensity exercise protocols.

The effects of HIIT and continuous physical exercise have rarely been compared to one another, and when they were compared, their protocols are usually considerably different (e.g. Kao et al., 2017), with the noted exception of the aforementioned study by Kao and colleagues (2018) where they employed duration-matched exercise protocols. Therefore, corroboration of the effects of HIIT and continuous physical exercise on declarative memory performance with a more stringent protocol is warranted. Subsequently, in Study 3, I utilised a HIIT protocol that was matched for energy output to a continuous moderate-intensity exercise protocol, which was consequently shortened and more closely matched in duration to the HIIT protocol (rather than comparing 3 min HIIT vs 30 min continuous moderate-intensity exercise). By doing so, any observable differences (if any) in performance scores between the two protocols would be less likely attributed to exercise duration and/or energy output mismatch and would instead be attributable to the phusical exercise protocol itself.

3.2 Wakeful rest

On a typical day, rest is considered a “waste of time” because it is thought as a period where an individual could be doing something productive instead. However, research into the effects of wakeful rest on memory suggests that rest may in fact play a significant role in memory consolidation (for review: Wamsley, 2019). This is likely the result of memory reactivation and consolidation that occurs specifically during resting periods with minimal attentional demand (Wamsley, 2019).

Wakeful rest can be categorised into two domains: active rest and passive rest. Passive rest is a period of wakeful rest void of any cognitive engagement (e.g. participants are typically sat down comfortably in a task-free unoccupied rest). Active rest, on the other hand, involves replacing the period of no cognitive engagement with a cognitive distractor task (e.g. solving simple mathematics, playing a game).

Research has shown that memory consolidation, in some measure, requires an offline brain state in which new encoding is reduced and consolidation is prioritised (Stickgold, 2005). This is evident in studies showing enhanced memory consolidation after sleep (Born & Wilhelm, 2012; Stickgold, 2005; Tucker et al., 2006). Importantly however, many of these studies compare these effects to the active form of wakeful rest, where cognitive distractor tasks are employed and keep the participants engaged during memory consolidation. While this comparison may be useful for a typical day-to-day setting, it does not account for the potential effects of passive wakeful rest, which more closely resembles an offline sleep state.

It has been shown that short periods of passive rest after encoding result in better memory consolidation in comparison to similar periods of active rest – i.e. periods spent performing post-encoding cognitive tasks (Brokaw et al., 2016; Dewar et al., 2012; Wamsley, 2019). Recently, studies are finding that passive rest may in fact be able to facilitate memory consolidation in a similar fashion to sleep, with its effects lasting for over one week. For example, compared to similar periods spent on completing a cognitive task, post-encoding passive rest has been shown to enhance declarative memory (Brokaw et al., 2016; Dewar et al., 2012), procedural memory (Humiston & Wamsley, 2018), as well as spatial and temporal memories (Craig, Dewar, Della Sala, & Wolbers, 2015).

As previously mentioned (section 1.1), two types of consolidation exist: systems-level and synaptic-level consolidation. Systems-level consolidation takes time, and thus, likely requires sleep to stabilise memories for the long-term, however, synaptic consolidation can stabilise memories without the need for sleep – at least in the short term (Wamsley, 2019). Yet, the initial stages of system consolidation are believed to start during the first few hours after learning (Wamsley, 2019), and given that these early stages of consolidation may require an offline brain state, this is likely taking place during wakeful rest where attentional demands are decreased. These studies suggest that even during wakeful rest, memory is preferentially consolidated during offline states – represented by reduced attentional demands – and not evenly apportioned throughout the entirety of wakefulness (Wamsley, 2019). Furthermore, this highlights the shared neurobiological features needed for successful consolidation between sleep and other offline states such as wakeful rest.

When discussing wakeful rest, it is important to highlight some of the resting-state EEG correlates of memory consolidation. Whilst there is a general consensus that memory is better retained after a full night of sleep (Brokaw et al., 2016), more recent studies are finding that a even a short nap as little as 6 min can lead to a memory-enhancing effect (Lahl et al., 2008). This raises the question of what allows for such short periods of sleep to enhance memory performance? Brokaw and colleagues suggest that that fast-acting offline consolidation mechanisms that do not require a full sleep cycle might be at play, or that consolidation is likely to occur during any state of wakefulness as long as the encoding of new information is at a minimum during the consolidation period (Brokaw et al., 2016). In their study Brokaw and colleagues confirmed that a short period of wakeful rest facilitates the consolidation of declarative memory and suggest two predictors for this effect. The authors suggest that an increase in slow oscillatory EEG rhythms and attenuated alpha rhythms may predict enhanced memory performance after a period of wakeful rest (Brokaw et al., 2016). They also identified that enhanced memory performance is associated with decreased attention to external factors (Brokaw et al., 2016).

Several studies show that wakeful rest affects memory in a similar manner to that of sleep. Specifically, short-wave ripples (SWRs), which describe oscillatory patterns that occur in the hippocampus and entorhinal cortex during immobility and sleep are involved in the consolidation of recently acquired labile memory traces (Girardeau et al., 2009). Jadhav and colleagues (2012) showed that blocking SWRs during wakeful rest results in reduced spatial memory (Jadhav et al., 2012). Ramadan and colleagues (2009) also showed that increased hippocampal SWRs during sleep enhance memory consolidation (Ramadan et al., 2009). This highlights one of the shared neurobiological mechanisms that underlie the effects of sleep and wakeful rest on memory.

Another of the shared neurobiological mechanisms between sleep and wakeful rest is the facilitation of memory consolidation via slow-wave oscillatory activity. Increased slow-wave oscillatory activity, specifically below 1 Hz, are linked to enhanced memory consolidation during sleep by promoting hippocampal-cortical communication (Brokaw et al., 2016; Wamsley, 2019). Brokaw and colleagues (2016) identified that low-frequency oscillations also facilitate memory retention during passive wakeful rest, which proposes that passive wakeful rest could enhance memory consolidation via similar neurophysiological mechanisms employed during sleep (Brokaw et al., 2016).

Interestingly, relative to sleep and passive wakeful rest, active wakeful rest is differentiated by increased levels of acetylcholine (Tucker et al., 2020; Wamsley, 2019). Acetylcholine is thought to modulate memory consolidation by facilitating hippocampal-cortical communication dynamics during offline states that are preferentially biased towards consolidation over new learning (Wamsley, 2019). This occurs through the binding of acetylcholine to presynaptic and postsynaptic neuronal receptors triggering an increase in growth factors such as BDNF (Maurer & Williams, 2017; Tucker et al., 2020; Wamsley, 2019).

Overall, this suggests that the effects of wakeful rest on memory stem from processes that may require some form of an offline brain state – or reduced attentional demand –to facilitate memory consolidation via the reactivation of recently acquired labile memories.

3.3 Transcranial direct current stimulation

The advent of modern brain stimulation techniques (for example, transcranial magnetic stimulation; TMS) has helped advance the field of neuropsychology. Advancements in neuroimaging techniques have led to a better understanding of the roles of different brain regions and subsequently, a better understanding for which regions should be targeted using brain stimulation techniques to induce changes in cognitive functions, motor functions and even sensory- or emotional functions (Utz et al., 2010).

Accordingly, many brain stimulation techniques have started to gain popularity, for instance, deep brain- and vagus nerve stimulation (Utz et al., 2010). The majority of these techniques, however, are expensive to use and many also invasive. By using brain stimulation techniques that are cheaper and easier to use, a faster understanding of neuropsychological functions could be elicited. This inspired the resurgence of the use of transcranial direct current stimulation (tDCS) as a tool to modulate cortical function and guide neuroplasticity (Nitsche, Boggio, Fregni, & Pascual-Leone, 2009; Nitsche et al., 2008).

tDCS induces a relatively weak current that flows through the cerebral cortex via electrodes placed (typically) on the scalp (Nitsche et al., 2009). Depending on the polarity of the stimulation, tDCS can induce cortical activity that is excitatory or inhibitory (Nitsche et al., 2008), as well as spontaneous neuronal activity (Nitsche et al., 2009).

When tDCS began its resurgence in the 1960s, studies started to show that anodal stimulation over the cortex increased spontaneous neuronal activity by depolarising the membrane. In contrast, cathodal stimulation decreased neuronal activity via membrane hyperpolarisation (Bindman, Lippold, & Redfearn, 1964; Creutzfeldt, Fromm, & Kapp, 1962; for review: Nitsche et al., 2009). These cortical changes, however, are not homogenously dependent on stimulation polarity. That is, whilst the majority of activations depend on the polarity of stimulation (anodal stimulation increases activity, cathodal decreases it), some neurons can be modulated in reverse direction (M. A. Nitsche et al., 2009; Utz et al., 2010). A study by Creutzfeldt and colleagues (1962) found that cortical changes can also be determined by the type of neurons, neuronal spatial orientation, and stimulation intensity (Creutzfeldt et al., 1962). Specifically, they found that neural activity coming from the deeper layers of the cat motor cortex was increased by cathodal stimulation and decreased by anodal stimulation. Creutzfeldt argued that this was a result of the spatial orientation of the neurons, which induced the reversal of current flow (Creutzfeldt et al., 1962).

The stimulation effects were shown to last well beyond the period of stimulation (for review: Utz et al., 2010). Subsequent studies found that these long-lasting effects are dependent on protein synthesis and modifications of intracellular cAMP and calcium levels (Hattori, Moriwaki, & Hori, 1990; Islam, Aftabuddin, Moriwaki, Hattori, & Hori, 1995; for review: Nitsche et al., 2008). Interestingly, pharmacological studies found that the effects of anodal tDCS are reduced, and in some cases completely abolished, by voltage-dependent ion channel blockers (e.g. carbamazepine) but showed no effect on hyperpolarisation from cathodal stimulation (for review: Utz et al., 2010). Furthermore, dextromethorphan, a non-competitive NMDA-receptor antagonist, was found to be able to diminish the long-term effects of tDCS for both anodal- and cathodal tDCS (Nitsche et al., 2003; Utz et al., 2010). The authors of these studies concluded that the short-term effects of tDCS are brought on by the polarisation effects of the neuronal membrane, whereas, the modulation of NMDA receptor strength is responsible for the long-lasting effects of tDCS (Utz et al., 2010). The NMDA-receptor-dependent long-lasting effects of tDCS share features with LTP and long-term depression (LTD), which underlie neural plasticity (Nitsche et al., 2008; Utz et al., 2010).

The majority of early studies administering tDCS in humans targeted the motor cortex due to the ease of monitoring cortical changes by transcranial magnetic stimulation (TMS)-induced motor evoked potentials (MEPs) (Nitsche et al., 2009). More recently, some tDCS studies targeting the motor cortex have found significant ergogenic effects on physical exercise performance, although the results have been relatively inconsistent. That being said, the results do lean towards a positive tDCS effect on physical exercise capacity (Angius et al., 2017). Okano and colleagues found that anodal tDCS improved maximal power output by approximately 4% in addition to a lower heart rate and rate of physical exertion (RPE) compared to a sham condition (Okano et al., 2015). The authors suggested that the observed performance increase could be a result of tDCS-induced modulation of insular cortex activity, which also consequently resulted in a reduced RPE (Angius et al., 2017; Okano et al., 2015). In contrast, Angius and colleagues did not observe an effect on exercise performance or changes in RPE, but instead found that anodal tDCS over the motor cortex led to a reduction in perceived pain during a cold pressor task (Angius et al., 2015). The authors suggested that tDCS montage could have resulted in the lack of an effect since the cathodal electrode was placed over the dorsolateral prefrontal cortex, which could have negated any benefits from the anodal electrode over the M1 motor cortex (Angius et al., 2015, 2017).

Whilst the majority of early studies administering tDCS in humans target the motor cortex, tDCS-induced modulation is not limited to that region. For example, studies have shown tDCS-induced modulation in areas such as the prefrontal cortex, which affects declarative memory (Javadi & Walsh, 2012), the occipital cortex, which affects perception and memory of faces (Barbieri et al., 2016), and the parietal cortex, which affects prestimulus alpha oscillations (Hsu et al., 2014).

tDCS over the dorsolateral prefrontal cortex (DLPFC), specifically, the left DLPFC, is of particular importance in this dissertation as it has been shown to play a role in long-term memory (Blumenfeld & Ranganath, 2006). For a detailed account of the role of the left DLPFC in long-term memory, and further details on tDCS, please see Chapter 3.

3.4 Brain-derived neurotrophic factor

Studies of learning and memory in animal models have identified several gene products necessary for molecular and cellular mechanisms underlying cognitive processes and behaviour (Cunha et al., 2010). Brain-derived neurotrophic factor (BDNF) is one of these gene products and is a protein belonging to a family of neurotrophic growth factors. BDNF is involved in the differentiation, maturation, and survival of neuronal populations during development (Bathina & Das, 2015; Bekinschtein et al., 2014). Evidence suggests that BDNF also regulates the structure and functions of different neuronal circuits throughout life as well as playing a vital role in learning and memory, particularly LTP (Bekinschtein et al., 2014; Cunha et al., 2010).

BDNF is an important molecule involved in several memory processes, such as the formation of different types of memories, and is critical for LTM maintenance (Bekinschtein et al., 2014). Its wide role in different types of memories and involvement in distinct memory stages points at BDNF as one of the likely targets to treat cognitive impairments (Bekinschtein et al., 2014).

Many animal studies have identified the role of BDNF in learning and memory. For example, increases in BDNF mRNA expression in the rat hippocampus following training in several memory tests (e.g. Morris water maze, radial arm maze) suggests that the regulation of BDNF activity is associated with hippocampal learning *in vivo* (Cunha et al., 2010;

Kesslak et al., 1998; Mizuno et al., 2000). BDNF is also highly expressed in other brain regions responsible for cognitive functions, and its regulation-by-learning also applies to these areas.

Studies using heterozygous knockout (KO) mice for BDNF, whereby one of two gene copies (alleles) is knocked out, showed learning deficits in the Morris water maze and in contextual fear conditioning (Cunha et al., 2010; Linnarsson et al., 1997; Liu, 2004). Additionally, the reduction of BDNF mRNA and protein in rats led to spatial learning impairment and LTP reduction (Cunha et al., 2010; Mizuno et al., 2000). Further, stopping the translation of endogenous BDNF prevented the consolidation of contextual fear conditioning, suggesting a crucial and causal role for BDNF in LTM processes (Cunha et al., 2010; Lee et al., 2004).

There is evidence supporting the role of BDNF in post-learning maintenance of LTM. Bekinschtein and colleagues (2007) showed that administering BDNF-blocking antibodies in the rat hippocampus within 12h after learning blocked memory retention by inhibiting protein synthesis (Bekinschtein et al., 2007). During this 12h period, administering mature BDNF reversed the inhibition of protein synthesis and restored memory retention (Bekinschtein et al., 2008). This suggests that BDNF is not only necessary, but also able to stabilise consolidation-like events needed for LTM maintenance.

Since its discovery, BDNF has become an important mediator of synaptic plasticity, as it not only contributes to LTP but also likely to be at the heart of plasticity-related processes underlying long-term memory. This is especially evident in studies similar to the aforementioned study by Bekinschtein and colleagues (2008), where the addition of BDNF leads to the restoration of learning in rats with endogenously depleted BDNF.

BDNF is also known to be stimulated by physical exercise, which further contributes to its association with learning and memory (Heinonen et al., 2014). This is achieved via exercise-induced increases in the synthesis and release of BDNF. During rest, BDNF is already being released from the brain, however, during exercise, this release increases by two- to threefold and contributes for a large majority of circulating BDNF (Heinonen et al., 2014). Several studies in both human and animal models have linked physical exercise to BDNF modulation and cognition (Coelho et al., 2013).

A positive correlation between exercise intensity and plasma levels of BDNF in young, healthy participants has been shown (Phillips et al., 2014). In line with this, a study by Knaepen and colleagues (2010) showed that high-intensity exercise protocols yield larger increases in circulating BDNF than lower intensity protocols (Knaepen et al., 2010). This suggests that, if BDNF were a mediator of the effects of physical exercise on cognitive performance, exercise intensity would be expected to have an effect of the behavioural outcomes (Chang et al., 2012; Knaepen et al., 2010). Furthermore, most continuous physical exercise studies have demonstrated a linear dose-response relationship between physical exercise intensity and BDNF concentration (for review: Chang et al., 2012; Knaepen et al., 2010). Therefore, I wanted to assess how an interval training, performed at a high intensity (HIIT) would impact BDNF expression.

Another important moderator is the timing of the cognitive test in relation to exercise as it has been shown to impact the effect of acute exercise on cognition (Lambourne & Tomporowski, 2010). Because physical exercise has transient effects on BDNF, the timing of cognitive tests may be crucial in terms of the effects mediated by BDNF (Chang et al., 2012).

3.5 Arousal and attention

Many studies investigating the effects of physical exercise on cognition stem from arousal theories, with the common assumption that cognitive performance depends on the allocation of energetical resources to meet task demands (Lambourne & Tomporowski, 2010). The methods used to modulate arousal levels have not been consistent, and therefore, depending on the approach taken, studies have found physical exercise to either facilitate or impair cognitive function (Lambourne & Tomporowski, 2010). Several researchers have demonstrated that acute physical exercise leads to increased peripheral levels of adrenaline and noradrenaline. Cortisol release modulates arousal by limiting corticotrophin releasing hormone (CRH) and adrenocorticotrophin hormone (ACTH). With regards to physical exercise, when the intensity or duration of an exercise task increases beyond a certain threshold, cortisol synthesis can no longer inhibit ACTH and CRH. This leads to significantly increased levels of arousal to the point where the limited neural resources are being allocated to the control of the exercise task instead of the cognitive task cognitive, resulting in compromised cognitive performance (Lambourne & Tomporowski, 2010). Lambourne and Tomporowski suggest that arousal influences bottom-up mental processes and enhances performance on cognitive tasks involving quick decisions, and then following exercise, it also enhances memory storage and encoding (Lambourne & Tomporowski, 2010).

Empirical studies suggest that arousal level follows an inverted-U relationship to cognitive performance. That is, as exercise-induced arousal level increases, so does task performance, but only up to a certain point. Beyond this threshold, task performance will deteriorate. Correspondingly, Kamijo and colleagues found that P300 amplitude decreased after a bout of high-intensity physical exercise but increased after a bout of moderate-intensity physical exercise. The authors indicated that these changes in P300 amplitude showed an inverted-U relationship with differences in physical exercise intensity, suggesting that the differences in physical exercise intensity influenced arousal level (Kamijo et al., 2004). Similarly, in their investigation, Arent and Landers assigned participants to one of eight arousal groups (between 20 – 90% of heart rate reserve) and found that optimal performance on a simple response time task was between 60 – 70% of maximum arousal (Arent & Landers, 2003). The authors claim that their findings support an inverted-U relationship between arousal and cognitive performance (Arent & Landers, 2003).

Physical exercise has also been found to enhance attention (Hillman et al., 2005). Some studies have also found that enhanced attention after a bout of coordinated exercise that involves the activation of the cerebellum, which besides motor functions, influences attention and memory, amongst other neurobehavioural systems (Budde et al., 2008). A study by Jois and colleagues investigated the effectiveness of Superbrain Yoga (SBY; a form of exercise that involves squatting and combines breathing and acupressure) on attention and found significant enhancements to selective attention after a bout of SBY, and suggested that this may be due to increased alpha wave activity in the brain (Jois et al., 2017). This is in line with other studies that also demonstrate increased alpha activity with enhanced attention (Chaire et al., 2020).

3.6 Summary

Many studies have compared the different effects of physical exercise on long-term memory. However, these studies typically employ varying intensities, durations and behavioural measures, with only a few providing direct comparisons between physical exercise and different types of rest. By providing a standardised design, this thesis, through six studies, compared different intensities (low, moderate, high) and modalities (continuous vs interval) of physical exercise, in order to determine the most effective physical exercise protocol for long-term memory enhancement, whilst also directly comparing it to two types of rest (active and passive rest). Furthermore, EEG was recorded during physical exercise to investigate any correlations between neural oscillatory activity and enhanced long-term memory performance. In addition to this, numerous studies have reported significant enhancing effects of transcranial direct current stimulation (tDCS) on long-term memory performance, and therefore, the effects of physical exercise and tDCS were also compared. This was also the first instance in which physical exercise and tDCS were combined into one intervention to investigate their combined effects on memory performance. Therefore, through the incorporation of neuroimaging and brain stimulation techniques, this research will look to further develop the neural understanding of physical exercise and long-term memory enhancement, as well as exploring how to leverage such information to explore combined interventions of acute physical exercise and brain stimulation.

Chapter 2: The effects of physical exercise and wakeful rest on long-term memory

1. Chapter Overview

Advancements in medicine and medical technologies have had a significant positive impact on global life expectancy. According to data collected by the United Nations Department of Economic and Social Affairs, it is predicted that life expectancy will substantially increase within the coming decades (83 years by 2100; up from 65 years in 1995). With age being a significant risk factor for neurodegenerative diseases (e.g. Alzheimer's disease), it is crucial that research into sustaining cognitive ability is not overlooked.

Although many studies have shown that physical exercise enhances memory performance by facilitating the consolidation of information (Coles & Tomporowski, 2008; Potter & Keeling, 2005; Winter et al., 2007), its effects on long-term memory are not distinct and remain contested. This can be attributed to a lack of consistent measurement methods across studies, such as exercise duration (e.g. acute or chronic), exercise intensity, exercise type (e.g. cycling, running, or swimming), and onset of exercise relative to encoding (e.g. before or after).

Similarly, wakeful rest enhances memory performance, with some studies showing that short bouts of wakeful rest may enhance certain memory domains (Craig et al., 2016; Craig & Dewar, 2018), even up to a week after encoding (Dewar et al., 2012). In this chapter, two types of rest will be investigated: passive wakeful rest (PR) and active wakeful rest (AR). PR is a period of rest that does not include any overt sensory or motor activity. Whereas, AR, aimed to replicate the mild form of interference we are subject to on a daily basis, is a period of rest that includes one or more cognitively stimulating tasks alongside physical rest, such as listening to music or playing video games (Wamsley, 2019).

Research into the cognitive benefits of physical exercise and wakeful rest is not only important for the preservation of memory and cognitive function but demonstrating these benefits to the general population can subsequently promote better lifestyles, especially eating habits, and bring attention to the importance of rest in the current climate of increased stress of work and daily routines.

Although many studies have investigated the different effects of physical exercise on long-term memory, further clarification into the most effective intensity and protocol is required. Furthermore, no study provides direct comparisons between physical exercise and different types of rest. Therefore, the purpose of this chapter was to compare the effects of different protocols of physical exercise and rest on long-term memory enhancement. Across three parallel studies (N=59), the extent that physical exercise and wakeful rest could modulate long-term memory performance was measured. This was achieved using the same old/new recognition memory task and an 80-90 min retention interval across all three studies. In the first study, the effects of three different intensities of physical exercise were examined in order to form a better understanding into the mechanisms of effects, since both the inverted-U and drive theories suggest that physical exercise intensity can influence the size of the effect. Several studies report enhanced memory consolidation via wakeful rest (Dewar, Alber, Cowan, & Della Sala, 2014; Mercer, 2015), therefore, for the second study, two types of wakeful rest (active and passive) were compared against the intensity with the best behavioural outcome from the first study. For the third study, the effects of interval training in the form of high-intensity interval training (HIIT) was compared against the most effective physical exercise intensity from the first study and the most effective type of wakeful rest from the second study. This is because the effects of HIIT and continuous physical exercise have rarely been compared to one another, and therefore, such an investigation into their effects on declarative memory performance will bring about a better understanding into the mechanisms of effects.

2. Introduction

2.1 Effects of physical exercise on long-term memory

The cognitive effects of acute physical exercise have attracted considerable attention in research during the last decade. Accordingly, this line of research has engendered great interest in the understanding of the effect of physical exercise on cognition and prompted numerous debates regarding its memory-enhancing capabilities. These debates are largely a by-product of inconsistent methodology across studies, such as physical exercise duration, physical exercise intensity, type of physical exercise, and onset- and temporal proximity of physical exercise relative to encoding. Such variability in literature has vacillated the cognitive-enhancing capacity of physical exercise, especially long-term memory. The physical exercise-memory relationship is complex and easily moderated by such variables. However, there is strong evidence supporting the notion that physical exercise has significant positive effects on cognitive function as a whole (Kramer & Colcombe, 2018; Voelcker-Rehage & Niemann, 2013; for a model, see Stimpson, Davison, & Javadi, 2018), although the means by which physical exercise elicits such enhancements remain rather ambiguous. The timing of physical exercise relative to encoding plays a key role in physical exercise-induced memory enhancement. Current research suggests that post-encoding physical exercise yields greater enhancements to memory performance compared to pre-encoding (Coles & Tomporowski, 2008) or mid-encoding (Loprinzi et al., 2019). However, some studies (Hötting et al., 2016) show no memory enhancement from post-encoding physical exercise.

2.2 Effects of passive wakeful rest on long-term memory

Many studies have highlighted the importance of sleep in facilitating better memory retention. Detailed investigations into the effects of sleep have attributed these enhancements to the process of offline memory consolidation (Brokaw et al., 2016; Stickgold, 2005). However, a large majority of these studies have compared the effects of sleep on memory to active waking control conditions, such as playing video games or performing cognitive distractor tasks (Wamsley, 2019). Yet, these conditions inherently interfere with the process of memory consolidation, and surprisingly, there are very few studies comparing the effects of sleep to a passive waking control (a state a minimal interference during wakefulness) (Brokaw et al., 2016; Wamsley, 2019).

There is strong evidence that post-encoding passive rest (PR) enhances memory (Craig et al., 2015; Dewar et al., 2012; Dewar, Alber, Cowan, & Della Sala, 2014; Humiston & Wamsley, 2018). For example, several studies (Cowan et al., 2005; Dewar et al., 2009) show that both young adults and elderly participants are able to better retain newly learned words if a period of PR as short as 10 min is introduced immediately after encoding than if encoding is immediately followed by sensorimotor or cognitive tasks (Dewar et al., 2012; Wamsley, 2019). However, the conditions in which such enhancements are induced are not yet fully understood and further research into the cognitive basis of memory enhancement is needed.

Neuroimaging studies have provided evidence for wakeful-rest-induced facilitation of memory retention in the form of slow neural oscillatory activity recorded from scalp EEG (Brokaw et al., 2016). Interestingly, these oscillations are similar to the oscillations thought to support memory consolidation during sleep (Wamsley, 2019). Dewar and colleagues highlight several animal studies showing that memory consolidation is linked with the spontaneous reactivation of recent encoding-related neural activity, and that this reactivation primarily takes place during sleep, where mobility is at a minimum (Dewar, Alber, Cowan, & Della Sala, 2014). In humans, this is further supported in neuroimaging studies where such reactivation is observed in PR, and a direct link between the level of reactivation and performance on a cognitive task is made (Dewar, Alber, Cowan, & Della Sala, 2014). Together, this suggests that, similar to sleep, wakeful rest (particularly PR) may enhance memory consolidation through offline reactivation and synaptic plasticity (Wamsley, 2019).

As previously discussed in Chapter 1, local cellular-level memory consolidation begins immediately after encoding and is able to stabilise the memory trace against interference for a few hours. This form of consolidation has been regularly demonstrated to occur during wakefulness. Conversely, systems-level reorganisation of memory is resistant to interference for longer periods but typically relies on sleep and other offline states. Like sleep, passive rest is also a form of offline processing as it is represented by periods of reduced attentional and cognitive demand (Brokaw et al., 2016; Wamsley, 2019). Further, because a lot of the neurophysiology associated with the facilitation of consolidation during sleep is also thought to be present during PR, it is thought that PR can enhance memory in a similar manner to the mechanisms employed during sleep (Brokaw et al., 2016; Wamsley, 2019). Collectively, this suggests that, in addition to facilitating cellular-level memory consolidation, passive rest can also facilitate the early stages of systems-level consolidation (Dewar, Alber, Cowan, & Della Sala, 2014). This is supported in a study by Tambini and Davachi (2013), where they emphasise that post-encoding processes occurring during wakeful rest may contribute to memory consolidation, especially during periods of reduced environmental stimulation that can allow for the expression of physiological mechanisms essential for consolidation (Tambini & Davachi, 2013).

As mentioned earlier, there is evidence that PR may facilitate cellular-level and systems-level memory consolidation through offline reactivation and synaptic plasticity. Similarly, under the interference and consolidation theories, there is a requisite of low post-encoding cognitive activity for optimal memory consolidation. As described by Underwood (1957), the interference theory states that the retention of newly acquired memories can be impaired via cognitive processing (interference) occurring before or after encoding (Underwood, 1957). Moreover, the degree of interference is directly linked to how temporally close it is to the newly encoded memories – where more forgetting is observed with smaller temporal distances between the interference and the memoranda (Ecker et al., 2015). This hypothesis is shared with the consolidation theory, which states that newly acquired memories are labile and require stabilisation through time in order to avoid forgetting (Ecker et al., 2015).

Taken together, this suggests that the absence of post-encoding memoranda (e.g. periods of reduced cognitive processing and demand) is likely to provide enhanced conditions for the consolidation process and reactivation of memories – analogous to the manner by which sleep facilitates memory consolidation (Wamsley, 2019). This further reiterates that memory is preferentially consolidated during offline brain states (Wamsley, 2019). However, other possibilities for the observed increase in memory retention from PR should be considered. Although unlikely, due to the significant drop in sensory processing and immobility, PR may provide participants with the inadvertent opportunity to wander off in reflective thought – thinking about their day, recent events, or more importantly, an opportunity to rehearse the recently acquired memories that are to be tested in a later recall task. However, PR-induced memory enhancements have been shown not to be dependent on intentional rehearsal of the learned material during the rest period. That is, PR-induced consolidation is sufficient to enhance long-term memory without the need for intentional rehearsal (Dewar, Alber, Cowan, Della Sala, et al., 2014; Roediger & Butler, 2011).

2.3 Effects of active wakeful rest on long-term memory

A rest in learning processes is a common everyday occurrence. Every task can be interrupted, preceded, or followed by a period of rest (Kuschpel et al., 2015), which is perceived as a form of respite from task-induced fatigue. However, such breaks may also have a significant effect on the performance at a later time (e.g., memory recall) (Kuschpel et al., 2015).

In contrast to passive wakeful rest where the period of rest does not include any overt sensory or motor activity, active wakeful rest includes one or more cognitively stimulating tasks alongside physical rest, such as listening to music, playing video games, or scrolling through various social media outlets (Wamsley, 2019). When AR is introduced after encoding, the applied cognitive activity may induce a form of interference to the consolidation processes of the original memory. The specific conditions for interference to take place are still contested, however, it is suggested that interference can be brought about by – (a) contextually overlapping memoranda that elicit competitive replacement, which is achieved with paradigms employing the cue-overload principle (Watkins & Watkins, 1975), which states that the efficacy of a functional retrieval cue declines in aiding recall when the number of to-be-remembered-items associated with that particular cue increases (Watkins & Watkins, 1975). Essentially, in order for a retrieval cue to be effective, it cannot be overloaded with too many memories as this will decrease the likelihood of prompting retrieval of any one memory. And (b) the use of cognitively demanding tasks that are contextually dissimilar to the original memoranda. This interferes with the consolidation process by reallocating brain resources originally employed for consolidation-related processes to the cognitively demanding tasks (Varma et al., 2017). That is to say, because brain resources are limited (Raichle & Gusnard, 2002), focusing on an ongoing, cognitively-demanding task, should lead to fewer resources being allocated towards task-irrelevant processes, which in this case would be the consolidation processes employed for the original memoranda (Varma et al., 2017). This is evident in studies using secondary learning or post-encoding cognitive tasks (which show increased forgetting when compared to PR) (Dewar et al., 2012; Varma et al., 2017).

Varma and colleagues (2017) report that all post-encoding tasks show an interference effect when compared to PR. They point out that this may be a result of interference studies only using tasks with complex and meaningful stimuli that use up a significant portion of the general resources available for cognitive processing thereby eliciting interference (Varma et al., 2017).

3. Hypotheses

3.1 Study 1

In this study, the effects of different intensities (low, moderate, high) of continuous, acute physical exercise were compared.

H1: Moderate-intensity physical exercise will yield a higher performance score on the old/new recognition task than low-intensity physical exercise.

H2: Moderate-intensity physical exercise will yield a higher performance score on the old/new recognition task than high-intensity physical exercise.

H3: There will be no observable difference in performance score between high-intensity physical exercise and low intensity physical exercise.

3.2 Study 2

In this study, continuous, moderate-intensity exercise was compared to passive rest and active rest.

H1: Passive wakeful rest (PR) will yield higher a performance score on the old/new recognition task than active wakeful rest (AR).

H2: Moderate-intensity physical exercise will yield a higher performance score on the old/new recognition task than AR.

H3: Moderate-intensity physical exercise will yield a higher performance score on the old/new recognition task than PR.

3.3 Study 3

In this study, continuous, moderate-intensity exercise was compared to HIIT and passive rest.

H1: Moderate-intensity physical exercise will yield a higher performance score on the old/new recognition task compared to PR.

H2: Moderate-intensity physical exercise will yield a higher performance score on the old/new recognition task compared to high-intensity interval training (HIIT), due to the physiological effects associated with higher-intensities and shorter retention intervals (Hötting et al., 2016).

H3: There will be no observable difference in performance score between HIIT and PR, because higher-intensities of physical exercise as well as periods of rest have been shown to enhance or retain memory performance after longer retention interval periods (e.g. 24h) (Hötting et al., 2016; Roig et al., 2012).

4. Methods

For a schematic overview of all three studies please see Figure 8.

4.1 Study 1

4.1.1 Participants.

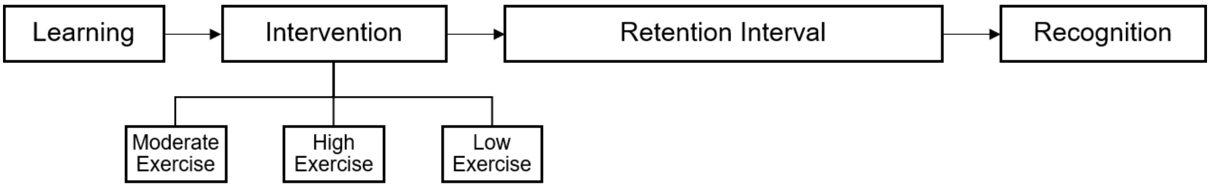
A total of 19 participants took part in this study (8 males; $M_{age} = 21.85$, $SD = 2.43$). All participants were naïve as to the aim of the study, spoke fluent English, German, French, or Spanish, and had normal or corrected-to-normal vision. Participants completed a questionnaire regarding their neurological and psychiatric health. Participants with any neurological or psychiatric disorders were excluded, as well as those taking any central-acting agents. Participants were also assessed using the Physical Activity Readiness Questionnaire (PARQ) to ensure that it was safe to perform the exercise tasks. All participants gave their written informed consent, and the study was given ethical approval by the Psychology Research Ethical Committee of the University of Kent.

4.1.2 Study Design.

This study followed a within-subject design with three interventions, with each intervention taking place one week apart and performed at the same time of day. Each experimental session consisted of a learning phase (encoding), intervention phase, retention interval, and a recognition phase (*Figure 5)*. During encoding, participants memorised 80 images of neutral objects. During the retention interval, participants watched episodes of the American sitcom "*Friends*". During the recognition phase, participants completed an old/new recognition task on 160 images (80 old, 80 new).

Figure 5.

Summary of study design for Study 1.



Note: Study 1 consisted of three interventions that were counterbalanced across participants. Each intervention took place seven days apart at the same time of day. Moderate-intensity exercise appears as occurring first, however, this is for demonstration purposes only.

4.1.3 Materials.

The study ran on a Windows 10 PC with a 17-inch monitor. A bank of 480 images of common objects with neutral valence was created using stimuli selected from two databases (Bank of Standardised Stimuli, and MIT Objects Stimuli) as well as from Google Image Search with an emphasis on neutral valence and simple images (e.g. banana, pen, lightbulb). 160 images were randomly selected for each experimental session, with no repetition of the images between sessions to avoid interference between each session. Stimuli presentation and response time were displayed and recorded using MATLAB (v2015b; MathWorks Company, Natick, MA) and Psychophysics Toolbox extensions (Brainard, 1997; Kleiner et al., 2007; Pelli, 1997).

4.1.4 Encoding.

Eighty images, split into two blocks of 40 images, were presented during encoding with a 1 min break in between the two blocks. Each stimulus was displayed on the monitor for 1s, with a fixation cross appearing in between for 2s. Participants were instructed to memorise the concept of the image (i.e. the object the image represents) rather than the actual image being displayed. This was to ensure that the memory task was a verbal memory task rather than a pictorial memory task. Given that verbal memory mostly relies on the left hemisphere and pictorial memory mostly relies on the right hemisphere, it was important that the left hemisphere was engaged to allow for unbiased comparisons given that the left DLPFC was targeted for the tDCS studies (Studies 4 – 6).

Prior to each experimental session (encoding and recognition), participants were asked to complete Stanford Sleepiness Scale to have a measure of their alertness (Hoddes et al., 1973; Maclean et al., 1992). The scale ranged between 1 (fully alert) and 6 (almost asleep).

4.1.5 Physical exercise.

Continuous physical exercise was performed at three intensities: low, moderate, and high. These intensities were defined within the parameters of the maximum heart rate (HR_{max}) and RPE score on the original Borg scale (1982) for each participant. Low intensity exercise was performed within 55-65% HR_{max} with reported RPE scores between 7 – 11, moderate intensity at 65-75% HR_{max} with reported RPE scores between 12 – 16, and high intensity at 75-85% HR_{max} with reported RPE scores between 17 – 20 (Borg, 1982; Centers for Disease Control and Prevention, 2020). HR_{max} was calculated using the formula developed by Tanaka and colleagues (Tanaka et al., 2001): $HR_{max} = 208 - (0.7 \times$ participant age). Heart rate was continuously monitored throughout the entirety of intervention using a Mio Fuse Heart Rate Monitor (Mio Global, US).

The intervention was split into six blocks of 4 min cycling on an ergonomic exercise bike (Stages SC3 Indoor Cycle, Stages Cycling, US) followed by 1 min rest. Just before the start of each block participants were instructed to maintain a randomly assigned cycling cadence (60-70 rpm, 65-75 rpm, 70-80 rpm) for the duration of the block. Cycling resistance was adjusted manually by the experimenter to keep the participants heart rate within the defined intensity. Participants were given 2 min to warm up and cool down at a low intensity and cadence. At the end of each exercise bout participants were asked to report their RPE score. Participants reporting an RPE score beyond the assigned limits (reported above) on the Borg Scale for two or more blocks were excluded (n = 1).

4.1.6 Retention Interval.

For a controlled period of retention, all participants watched the American TV sitcom "*Friends*" for a duration of 50 min.

4.1.7 Recognition.

During the recognition phase, 160 images were presented. Eighty of these were previously shown during the learning phase (old stimuli) and 80 were never before seen (new stimuli). Similar to the learning phase, these stimuli were presented in two blocks (80 images per block) with 1 min break in between each block. Each image was presented on the monitor until the participants identified it as old or new using the left or right arrow key on the keyboard. Participants were instructed to respond as accurately and as quickly as possible.

4.1.8 Statistical Analysis.

The data were analysed using SPSS (v19; LEAD Technologies, Inc., Charlotte, NC). Old and new image accuracy were analysed separately. One-way repeated measures of analysis of variance (rANOVA) was used to analyse the main effect of intervention with percentage accuracy in recognition of the old/new words, including reaction time for the old/new words. Significant threshold of $p < 0.05$ was chosen. Following significant main effect of condition, post-hoc paired-sample t-tests were run for performance accuracy of old images (e.g. comparison of moderate-intensity exercise vs. high-intensity exercise). False discovery rate (FDR) was used for correction for multiple comparisons for post-hoc tests. Participants who have scored less than 55% on the old/new recognition were excluded from analysis (n = 0).

4.2 Study 2

4.2.1 Participants.

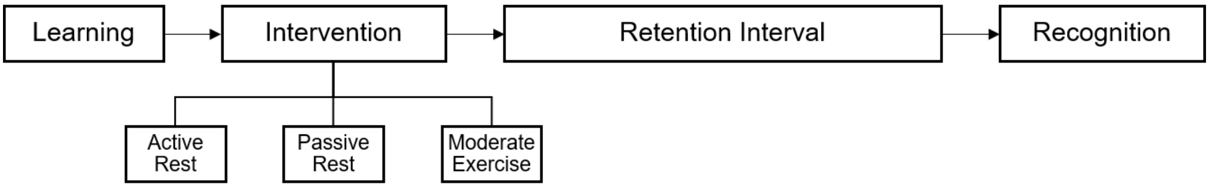
A total of seventeen participants took part in this study (7 males; $M_{age} = 19.77$, $SD = 1.27$). All participants were naïve as to the aim of the study, spoke fluent English, German, French, or Spanish, and had normal or corrected-to-normal vision. Participants completed a questionnaire regarding their neurological and psychiatric health. Participants with any neurological or psychiatric disorders were excluded, as well as those taking any central-acting agents. Participants were also assessed using the Physical Activity Readiness Questionnaire (PARQ) to ensure that it was safe to perform the exercise tasks. All participants gave their written informed consent, and the study was given ethical approval by the Psychology Research Ethical Committee of the University of Kent.

4.2.2 Study Design

Study design was identical to that of Study 1 (see section 4.1.2) (*Figure 6*).

Figure 6.

Summary of study design for Study 2.



Note: Study 2 consisted of three interventions that were counterbalanced across participants. Each intervention took place seven days apart at the same time of day. Active rest appears as occurring first, however, this is for demonstration purposes only.

4.2.3 Materials.

Materials used were identical to that of Study 1 (see section 4.1.3).

4.2.4 Encoding.

Encoding phase was identical to that of Study 1 (see section 4.1.4).

4.2.5 EEG Recording.

EEG was recorded during the entirety of the physical exercise session. Details of the methods and results are discussed in Chapter 4.

4.2.6 Interventions.

4.2.6.1 Physical exercise.

Physical exercise protocol was identical to that of the moderate intensity physical exercise protocol in Study 1 (see section 4.1.5). Participants reporting an RPE score below 12 or more than 16 on the Borg Scale for two or more blocks were excluded (n = 1).

4.2.6.2 Active rest.

The active rest intervention contained a cognitive task simulating the cadence thresholds on the physical exercise intervention. Participants were required to monitor and maintain a fluctuating number displayed on the monitor within a certain range. Similar to the continuous physical exercise intervention, this intervention consisted of six blocks of a 4 min task and 1 min rest, for a total duration of 30 min. At the beginning of each block, a range (60-70, 65-75, 70-80) was given to the participant in random order. Their task was to monitor and keep the fluctuating number displayed on the monitor within the specified range: press down or up arrow-key when the number went above or below the range, respectively.

4.2.6.3 Passive rest.

In the passive rest intervention, participants were asked to sit quietly and comfortably on a chair for 30 min with their eyes open to ensure they did not fall asleep. This type of rest intervention was chosen as it has been shown to significantly reduce cognitive interference (Craig & Dewar, 2018; Dewar, Alber, Cowan, Della Sala, et al., 2014). Participants were regularly monitored so as to ensure they did not fall asleep. At the end of the session (after the recognition phase), participants were asked what they did during the rest period to identify whether they rehearsed the stimuli or not. Participants who rehearsed (*N* = 1) were excluded from analysis.

4.2.7 Retention Interval.

Retention interval was identical to that of Study 1 (see section 4.1.6).

4.2.8 Recognition.

Recognition phase was identical to that of Study 1 (see section 4.1.7).

4.2.9 Statistical Analysis.

Statistical analysis was run in an identical manner to that of Study 1 (see section 4.1.8). Participants who have scored less than 55% on the old/new recognition were excluded from analysis (n = 1).

4.3 Study 3

4.3.1 Participants.

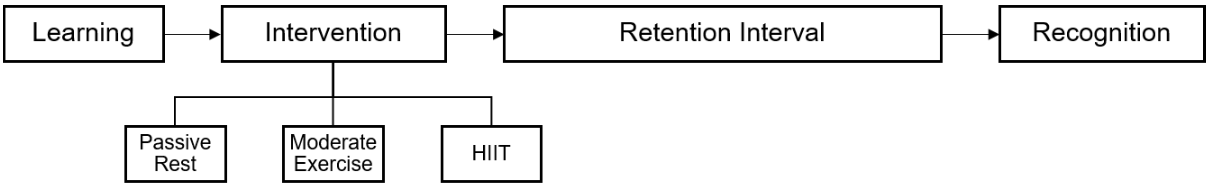
A total of twenty-three participants took part in this study (3 males; M_{age} = 19.62, *SD* = 1.51). All participants were naïve as to the aim of the study, spoke fluent English, German, French, or Spanish, and had normal or corrected-to-normal vision. Participants completed a questionnaire regarding their neurological and psychiatric health. Participants with any neurological or psychiatric disorders were excluded, as well as those taking any central-acting agents. Participants were also assessed using the Physical Activity Readiness Questionnaire (PARQ) to ensure that it was safe to perform the exercise tasks. All participants gave their written informed consent, and the study was given ethical approval by the Psychology Research Ethical Committee of the University of Kent.

4.3.2 Study Design

Study designed was identical to that of Study 1 (see section 4.1.2) (*Figure 7*).

Figure 7.

Summary of study design for Study 3.



Note: Study 3 consisted of three interventions that were counterbalanced across participants. Each intervention took place seven days apart at the same time of day. Passive rest appears as occurring first, however, this is for demonstration purposes only.

4.3.3 Materials.

Materials used were identical to that of Study 1 (see section 4.1.3).

4.3.4 Encoding.

Encoding phase was identical to that of Study 1 (see section 4.1.4).

4.3.5 Interventions.

4.3.5.1 Physical exercise.

Physical exercise protocol was identical to that of moderate-intensity protocol of Study 1 with the exception of duration (see Section 4.3.5.2 below for details). Participants reporting an RPE score below 12 or more than 16 on the Borg Scale for two or more blocks were excluded (n = 0).

4.3.5.2 High-intensity interval training.

The high-intensity interval training (HIIT) intervention consisted of four blocks of 30s cycling and 1 min rest, for a total duration of 6 min. Participants were instructed to cycle as fast as possible throughout the cycling period. The four blocks of 30s cycling were decided based on a pilot study in which participants in two separate sessions (*N = 21*) were asked to cycle for six blocks of 30s as fast as possible or cycle for two blocks of 3 min at a moderate intensity. Two blocks of 3 min moderate-intensity exercise were calculated based on previous data from Study 1. Four blocks of 30s HIIT resulted in a similar total energy expenditure as the two blocks of 3 min moderate-intensity exercise as measured by the power-meter on the cycle ergometer (energy exerted HIIT *Mean(SD) =25.476 (8.829) KJ;* Moderate-intensity = 27.666 (9.355); energy expenditure with 24% human energy efficiency (Marsh et al., 2000; Hopker et al. 2009) HIIT = 106.15 (36.788) KJ, Moderate intensity = 115.275 (38.979) KJ; t(20) = 1.182, *p* = 0.251).

4.3.5.3 Passive Rest.

Passive rest intervention was identical to that of Study 2 (see section 4.2.6.3).

4.3.6 Retention Interval.

Retention interval was identical to that of Study 1 (see section 4.1.6).

4.3.7 Recognition.

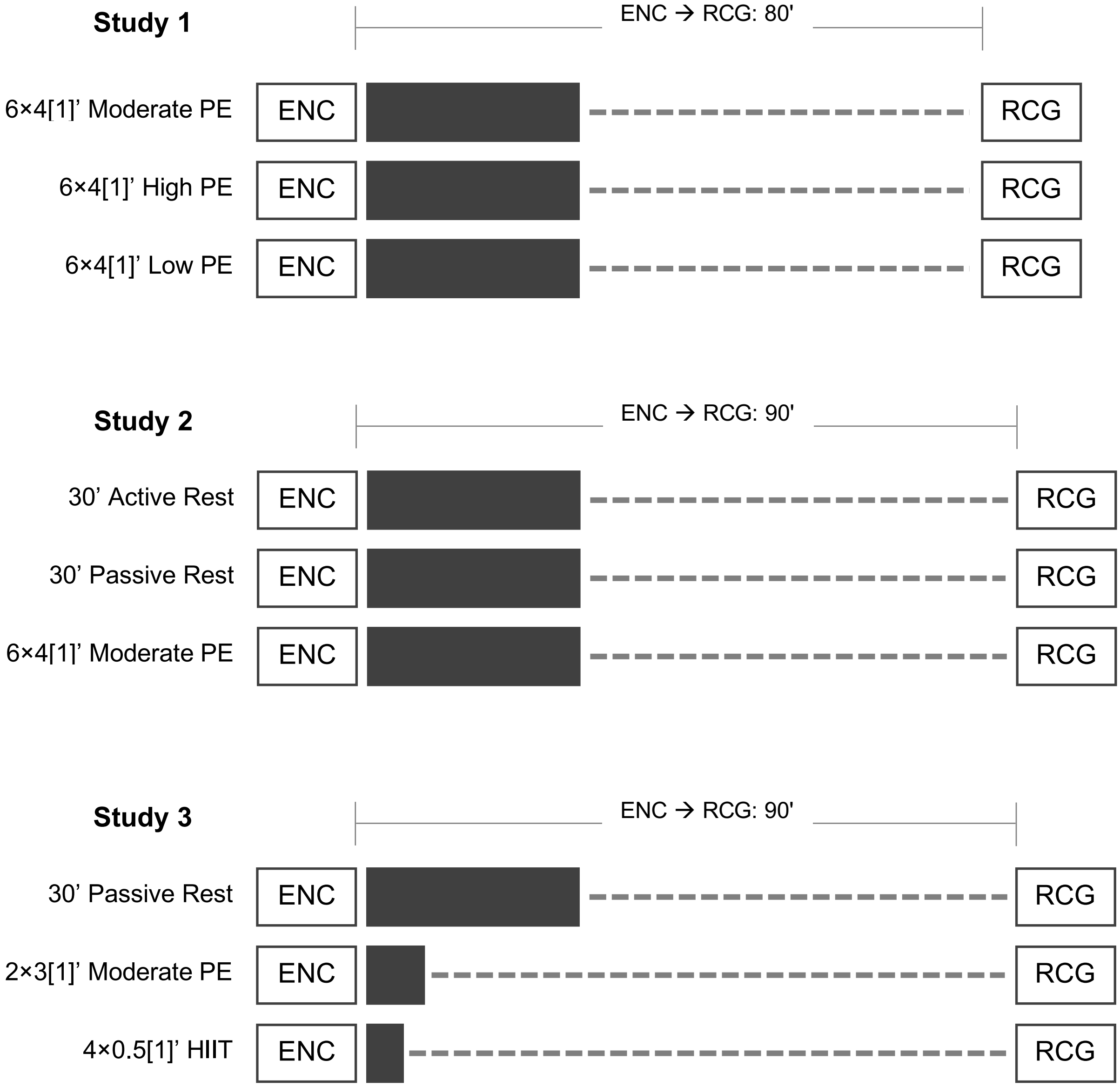
Recognition phase was identical to that of Study 1 (see section 4.1.7).

4.3.8 Statistical Analysis.

Statistical analysis was run in an identical manner to that of Study 1 (see section 4.1.8). Participants who have scored less than 55% on the old/new recognition were excluded from analysis (n = 0).

Figure 8.

Schematic of interventions for studies 1 – 3.



Note: A schematic was created to provide an overview of all three studies, including a visual representation of intervention duration. ENC: Encoding. RCG: Recognition. PE: continuous physical exercise. HIIT: High-intensity interval training. Black bars: visual representation of intervention duration. Dashed lines: retention interval. x[y]': x duration (min) of each block of PE, y rest (min) in between each block. Intervention order was randomised for all studies.

5. Results

Table 2 summarises the descriptive statistics for all three studies. Table 3 summarises the rANOVA that were run for each study. Table 4 and Figure 9 summarise post-hoc comparisons between different intervention conditions. Across the three studies, analyses showed significant main effect of condition for the recognition accuracy of the old images (ps < 0.026, $\eta_p^2 > 0.154$), but not new images (ps > 0.095). No effect was observed for the reaction time (ps > 0.191).

Ratings of Stanford Sleepiness Scale were also analysed for each study. All reported ratings were between 1 and 3 in all experimental sessions for studies 1 – 3. Three 3 × 2 rANOVA were run on the ratings for the three studies with condition and session (encoding/recognition) as within subject factors. These analyses showed no significant main or interaction effect (ps > 0.30). Order effect analysis was also run (Table 5). No pattern in favour of one intervention order over another was observed for studies 1 – 3 ($p > 0.05$). Power output data including mean heart rate is summarised in Table 6.

5.1 Study 1

Analysis revealed a statistically significant effect on performance accuracy scores of old images, $F(2,36) = 4.503$, $p = 0.018$, $\eta_p^2 = 0.200$. No significant effects were observed for reaction time, $F(2,36) = 1.732$, $p = 0.191$, $\eta_p^2 = 0.088$.

A paired sample t-test was run on a sample of 19 participants to determine whether there was a significant mean difference between performance accuracy scores between each intervention. The moderate-intensity physical exercise intervention produced a higher mean score (88.496) compared to high-intensity intervention (82.105); a statistically significant increase of 6.391 (95% CI, 2.590 to -9.439), $t(18) = 3.691$, $p = 0.002$, $d = 0.847$, thereby rejecting the null hypothesis and accepting the alternative hypothesis (H1). This sample size enabled me to achieve > 0.7 power to detect an effect size of Cohen's $d = 0.847$ at two-tailed $\alpha = 0.05$.

Moderate-intensity exercise produced a higher mean score (88.496) compared to low-intensity exercise (82.481), a marginally significant (after FDR correction) increase of 6.015 (95% CI, 0.439 to -12.342), $t(18) = 2.256$, $p = 0.037$ (significance corrected for multiple comparisons using FDR = 0.011), $d = 0.518$. This sample size enabled me to achieve > 0.3 power at two-tailed $\alpha = 0.05$. It was hypothesised that moderate-intensity physical exercise would yield a statistically significant increase in memory performance score compared to low-intensity physical exercise, therefore, this result fails to reject the null hypothesis.

There were no statistically significant differences in performance accuracy between the high-intensity and low-intensity exercise interventions (95% CI, -4.961 to -5.713), $t(18) = 3.691$, $p = 0.884$, $d = 0.034$.

5.2 Study 2

Analysis revealed a significant effect on performance accuracy scores of old images, $F(2,32) = 4.621$, $p = 0.017$, $\eta_p^2 = 0.224$. No significant effects were observed for reaction time, $F(2,32) = 1.206$, $p = 0.313$, $\eta_p^2 = 0.070$.

A paired sample t-test was run on a sample of 17 participants to determine whether there was a significant mean difference between performance accuracy scores between each intervention. The moderate-intensity physical exercise intervention produced a higher mean score (81.985) compared to the active rest intervention (75.294); a statistically significant increase of 6.691 (95% CI, 2.244 to -11.137), $t(16) = 3.190$, $p= 0.006$, $d = 0.774$, thereby rejecting the null hypothesis and confirming the alternative hypothesis (H2). This sample size enabled me to achieve > 0.5 power to detect an effect size of Cohen's $d = 0.774$ at two-tailed $\alpha = 0.05$.

Moderate-intensity exercise produced a higher mean score (81.985) compared to passive rest (77.794), a nonsignificant increase of 4.191 (95% CI, -0.095 to -8.478), $t(16) = 2.0732$, $p= 0.055$, $d = 0.503$, thereby failing to reject the null hypothesis.

There were no statistically significant differences in performance accuracy between the active rest and passive rest interventions (95% CI, -2.843 to -7.843), $t(16) = 0.992$, $p= 0.336$, $d = 0.241$.

5.3 Study 3

Analysis revealed a significant effect on performance accuracy scores of old images, $F(2,44) = 3.991$, $p = 0.026$, $\eta_p^2 = 0.154$. No significant effects were observed for reaction time, $F(2,44) = 0.889$, $p = 0.418$, $\eta_p^2 = 0.039$.

A paired sample t-test was run on a sample of 23 participants to determine whether there was a significant mean difference between performance accuracy scores between each intervention. The moderate-intensity physical exercise intervention produced a higher mean score (77.337) compared to the passive rest intervention (71.467); a statistically significant increase of 5.870 (95% CI, 1.482 to -10.256), $t(22) = 2.775$, $p= 0.011$, $d = 0.579$, thereby rejecting the null hypothesis and confirming the alternative hypothesis. This sample size enabled me to achieve > 0.4 power to detect an effect size of Cohen's *d* = 0.579 at two-tailed ɑ = 0.05.

Moderate-intensity exercise produced a higher mean score (77.337) compared to HIIT (74.348), a nonsignificant increase of 2.989 (95% CI, -0.951 to -6.930), *t*(22) = 1.573, *p*= 0.130, *d* = 0.328, thereby failing to reject the null hypothesis.

There were no statistically significant differences in performance accuracy between the HIIT and passive rest interventions (95% CI, -1.692 to -7.453), *t*(22) = 1.306, *p*= 0.205, *d* = 0.272.

Table 2.

Summary of descriptive statistics for studies 1 – 3.

Study	Measure	Condition	Old images	New images	d'
Study 1	Acc. (%)	Low PE	82.481 [3.032]	92.932 [1.611]	2.515 [1.011]
		Moderate PE	88.496 [1.596]	92.782 [1.512]	2.834 [1.085]
		High PE	82.105 [2.498]	92.030 [1.383]	2.481 [1.161]
	RT (s)	Low PE	1.56 [0.107]	1.938 [0.179]	
		Moderate PE	1.390 [0.077]	1.738 [0.124]	
		High PE	1.427 [0.090]	1.784 [0.147]	
Study 2	Acc. (%)	Moderate PE	81.985 [2.874]	88.824 [3.063]	2.552 [1.232]
		Active Rest	75.294 [3.287]	84.926 [3.102]	2.081 [1.099]
		Passive Rest	77.794 [3.614]	90.074 [2.553]	2.235 [1.183]
	RT (s)	Moderate PE	1.344 [0.089]	1.628 [0.109]	
		Active Rest	1.530 [0.138]	2.069 [0.422]	
		Passive Rest	1.407 [0.164]	1.694 [0.191]	

Study 3	Acc. (%)	Moderate PE	77.337 [2.630]	83.859 [3.011]	1.978 [1.103]
		HIIT	74.348 [2.485]	84.620 [2.363]	1.773 [0.829]
		Passive Rest	71.467 [2.076]	82.717 [2.614]	1.779 [0.830]
	RT (s)	Moderate PE	1.219 [0.063]	1.400 [0.075]	
		HIIT	1.354 [0.100]	1.428 [0.085]	
		Passive Rest	1.317 [0.100]	1.393 [0.103]	

Note. (mean [SD]) split over old images and new images. RT: Reaction Time (s). PE: Physical Exercise. HIIT: High-intensity Interval Training. d': D prime

Table 3.

Summary of rANOVA for studies 1 – 3 separated by old images and new images, performance accuracy and reaction time (RT).

Study		Old Images	New Images
Study 1	Accuracy	$F(2,36)=4.503$, $p=0.018$, $\eta_p^2=0.200$*	$F(2,36)=0.299$, $p=0.743$, $\eta_p^2=0.016$
	RT	$F(2,36)=1.732$, $p=0.191$, $\eta_p^2=0.088$	$F(2,36)=1.266$, $p=0.294$, $\eta_p^2=0.066$
Study 2	Accuracy	$F(2,32)=4.621$, $p=0.017$, $\eta_p^2=0.224$*	$F(2,32)=2.540$, $p=0.095$, $\eta_p^2=0.137$
	RT	$F(2,32)=1.206$, $p=0.313$, $\eta_p^2=0.070$	$F(2,32)=1.111$, $p=0.341$, $\eta_p^2=0.065$
Study 3	Accuracy	$F(2,44)=3.991$, $p=0.026$, $\eta_p^2=0.154$*	$F(2,44)=0.560$, $p=0.575$, $\eta_p^2=0.025$
	RT	$F(2,44)=0.889$, $p=0.418$, $\eta_p^2=0.039$	$F(2,44)=0.114$, $p=0.892$, $\eta_p^2=0.005$

Note. *$p<0.05$.

Table 4.

Summary of post-hoc paired-sample t-tests for performance on old images for studies 1 – 3.

Study	Comparison	t	p	Cohen's d	95% CI
Study 1	Moderate PE vs High PE	t(18) = 3.691	*p* = 0.002*	*d* = 0.847	2.590 –9.439
	Moderate PE vs Low PE	t(18) = 2.256	*p* = 0.037†	*d* = 0.518	0.439–12.342
	High PE vs Low PE	t(18) = 0.148	*p* = 0.884	d = 0.034	−4.961–5.713
Study 2	Moderate PE vs Active Rest	t(16) = 3.190	*p* = 0.006*	d = 0.774	2.244–11.137
	Moderate PE vs Passive Rest	t(16) = 2.0732	*p* = 0.055	d = 0.503	-0.095–8.478
	Active Rest vs Passive Rest	t(16) = 0.992	*p* = 0.336	d = 0.241	−2.843–7.843
Study 3	Moderate PE vs HIIT	t(22) = 1.573	p = 0.130	d = 0.328	-0.951 –6.930
	Moderate PE vs Passive Rest	t(22) = 2.775	*p* = 0.011*	d = 0.579	1.482–10.256
	HIIT vs Passive Rest	t(22) = 1.306	p = 0.205	d = 0.272	−1.692–7.453

Note. *p<0.011 significance corrected for multiple comparison using false discovery rate (FDR). † approaching significance based on FDR. PE: Physical Exercise. HIIT: High-intensity Interval Training.

Table 5.

Order effect analysis for studies 1 – 3.

Study	**Effect**	**F**	***p***	η_p^2
Study 1	Intervention	F(2,34)=0.784	0.465	0.044
	Order	F(1,17)=0.300	0.591	0.017
	Intervention × Order	F(2,34)=0.075	0.928	0.004
Study 2	Intervention	F(2,30)=0.796	0.460	0.050
	Order	F(1,15)=0.069	0.796	0.005
	Intervention × Order	F(2,30)=0.121	0.886	0.008
Study 3	Intervention	F(2,42)=4.275	0.020	0.169
	Order	F(1,21)=0.912	0.350	0.042
	Intervention × Order	F(2,42)=2.234	0.120	0.096

Table 6.

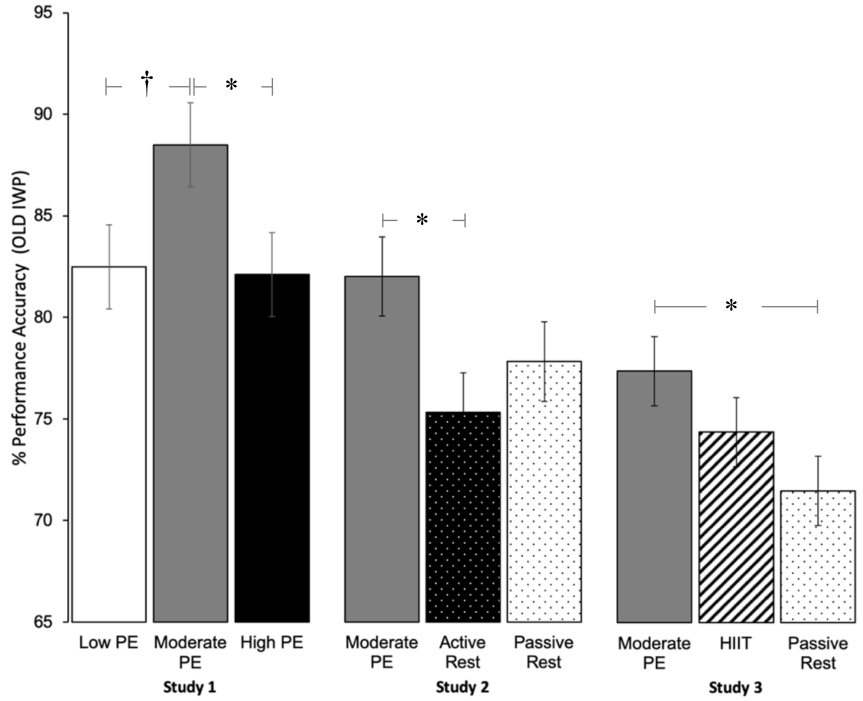
Summary of mean heart rate, power and energy for studies 1 – 3.

Study	Intervention	Heart rate (BPM)	Power (Watts)	Energy (Joules)
Study 1	Low Intensity PE	87.10 (19.48)	11.71 (10.10)	16868.57 (14537.18)
	Moderate Intensity PE	117.95 (19.96)	65.43 (33.74)	94217.14 (48587.08)
	High Intensity PE	134.33 (5.65)	99.57 (44.41)	143382.86 (63948.93)
Study 2	Moderate Intensity PE	111.71 (13.84)	65.93 (23.28)	94937.14 (33517.18)
Study 3	Moderate Intensity PE	108.54 (7.26)	47.76 (17.42)	17193.91 (6274.54)

Note: All values are mean (SD) of median measurements. Measurements occurred once every second (1 Hz).

Figure 9.

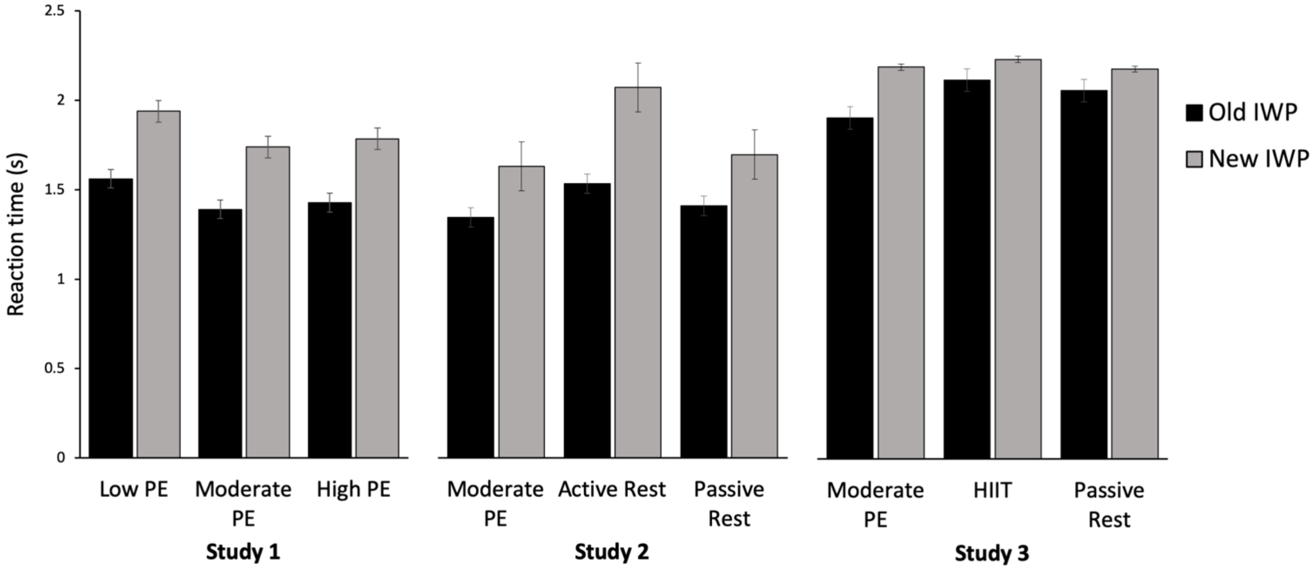
Performance accuracy for studies 1 – 3 split over different interventions.



Note: *p<0.011 significance corrected for multiple comparison using false discovery rate (FDR); †p=0.037 approaching significance based on FDR. Error bars represent one standard error of the mean.

Figure 10.

Reaction time scores for studies 1 – 3 split over different interventions.



Note: Error bars represent one standard error of the mean.

6. Summary

The aim of this chapter was to determine the most effective post-encoding protocol of physical exercise on long-term memory enhancement, whilst also directly comparing it to two types of wakeful rest. To investigate these aims, a series of three studies were run where performance accuracy on an old/new recognition task was assessed.

6.1 Study 1

The first study examined which of the three intensities of physical exercise (low, moderate, high) would yield the highest average performance accuracy score on an old/new recognition task. Physical exercise intensity was the focus of Study 1 in order to form a clearer understanding into the mechanisms of effects, as both the inverted-U and drive theories suggest that physical exercise intensity can influence the size of the effect. Results suggest that post-encoding, moderate-intensity physical exercise yields a significantly higher performance accuracy score than low-intensity and high-intensity physical exercise, which confirms my primary hypothesis for Study 1. Additionally, there were no observable differences in performance accuracy scores between low-intensity and high-intensity physical exercise, confirming my secondary hypothesis. Given the significant enhancement in performance accuracy score as a result of moderate-intensity physical exercise compared to low- and high-intensity physical exercise, it can be stated that moderate-intensity physical exercise significantly enhances long-term memory performance over low-intensity and high-intensity physical exercise. These findings are in line with several studies showing enhanced long-term memory performance after a bout of moderate-intensity physical exercise (Coles & Tomporowski, 2008; Pesce et al., 2009). The results further indicate that high-intensity physical exercise yields the lowest average performance accuracy score. This is similar to findings described by Loprinzi (2018), where he indicates that post-encoding, high-intensity physical exercise may not associate with long-term memory function (Loprinzi, 2018).

6.2 Study 2

The aim of the second study was to expand on the findings of Study 1. Study 1 showed the post-encoding moderate-intensity physical exercise enhances long-term memory performance significantly more than low-intensity and high-intensity physical exercise. Additionally, several studies (Dewar, Alber, Cowan, & Della Sala, 2014; Mercer, 2015) report enhanced memory consolidation via wakeful rest (for review see, Wamsley, 2019). On this basis, Study 2 compared the memory-enhancing effect of moderate-intensity physical exercise against two types of wakeful rest: passive and active rest. I hypothesised that (a) moderate-intensity physical exercise would yield a greater score than both passive- and active rest, and (b), passive rest would yield a significantly greater average performance accuracy score on the old/new recognition task compared to active rest.

In line with the primary hypothesis, the findings indicate that performance accuracy score is significantly higher for moderate-intensity physical exercise compared to active rest and approaching significance when compared to passive rest (p =0.055). Given that retroactive interference has been shown to hinder memory consolidation, I hypothesised that passive rest would outperform active rest on the old/new recognition task. However, contrary to this hypothesis, no observable differences in performance accuracy scores were detected between active rest and passive rest.

6.3 Study 3

In Study 1, memory performance on the old/new recognition task following continuous moderate-intensity physical exercise was significantly better than that of low-intensity or high-intensity physical exercise. Additionally, in Study 2, there was no significant difference in memory performance between moderate-intensity physical exercise and passive rest. For that reason, the aim of the Study 3 was to compare the effects of continuous moderate-intensity physical exercise, passive rest, and an interval-type of physical exercise known as high-intensity interval training (HIIT) on memory consolidation. Contrary to the results from Study 2, results from Study 3 show that moderate-intensity physical exercise significantly enhanced memory retention compared to passive rest (p = 0.011). There were no observable differences between moderate-intensity physical exercise and HIIT (p = 0.130), or between HIIT and passive rest (p = 0.205).

It is important to note two key differences. First, performance accuracy score of moderate-intensity physical exercise in Study 1 (88.496) is considerably higher than that of

Study 2 (81.985) and Study 3 (77.337). The second difference is in results comparing moderate-intensity physical exercise and passive rest between Study 2 and Study 3. In Study 2, performance accuracy score for moderate-intensity physical exercise was no different to passive rest. However, in Study 3, performance accuracy score of moderate-intensity exercise was significantly better than passive rest ($p = 0.011$). This could be attributed to the increased sample size between the two studies ($N = 17$ [Study 1]; $N = 23$ [Study 2]). Taken together, these results further support the positive influence of moderate-intensity physical exercise on memory consolidation.

To the best of my knowledge, no study has investigated the effects of post-encoding HIIT on long-term memory. Subsequently, the results from this study provide an interesting addition to the current literature regarding how post-encoding HIIT can influence memory. The results indicate no difference in memory performance between the HIIT and passive rest interventions. This falls in line with the hypothesis and, when factoring in the duration of the retention interval for this study, also falls in line with the current literature.

6.4 Considerations

Performance accuracy scores between studies displayed some degree of variability. This may be due to differences in the duration of retention interval, individual differences in response to physical exercise, as well as differences in baseline cognitive abilities and motivation to complete the tasks (Katz et al., 2017). This highlights the need to investigate other modulating factors such as fitness level, general cognitive abilities, and motivation. Additionally, further participant screening, such as screening for anxiety or habitual physical activity, may provide a deeper understanding of how emotional states or fitness levels can influence how physical exercise modulates long-term memory.

Across all three studies, physical exercise interventions were performed on a cycle ergometer. Whilst this has shown to effectively enhance memory performance, it is important to consider other forms of exercise, including resistance training (Northey et al., 2018), treadmill running (Delancey et al., 2018) or yoga (Yogesh et al., 2012).

The active rest protocol used in Study 2 employed a simple cognitive distractor task for the duration of the rest period. It would be of interest to investigate the effect on memory performance of different distractor tasks. For example, it would be interesting to compare active rest conditions with varying degrees of cognitive engagement and which utilise different tasks such as a puzzle or video game. Furthermore, modifying the degree of contextual similarity of the distractor task from the encoding task could provide further insight into the mechanisms of active-rest-induced interference.

Because participants completed three sessions in a study, the impact of repeated sessions on memory performance should be discussed. Whilst each session had a different intervention, the cognitive task used remained the same. With repeated testing, practice effects may occur and consequently complicate the interpretation of the results. Practice effects could increase memory performance scores for a number of reasons such as becoming familiar with the cognitive task and/or the testing environment, and consequently, a reduced anxiety (Bartels et al., 2010). If practice effects are not taken into consideration, this may result in overestimating intervention effects. Practice effects may be reduced by applying alternate forms of the same cognitive task (Benedict & Zgaljardic, 1998), fewer repetitions, or longer intertest intervals (Bartels et al., 2010). In the case of these studies, intertest interval was set at one week. This was the realistic maximum and optimal period given the time constraints participants (undergraduate students) were in to obtain their credits before end of term as well as a good balance that allows enough time to recruit more participants. Fewer repetitions could have been achieved if the three interventions per study were split into three separate studies. For example, in Study 1, instead of having one participant perform all three physical exercise intensities (three total repetitions), the study could have been split into three separate studies (low- vs moderate-intensity; low- vs high-intensity; and moderate- vs high-intensity) thereby reducing repetition down to two total repetitions.

Lastly, with regards to the order effect analysis, studies 1 and 2 have come up as non-significant for intervention effect, as opposed to significant before this analysis was run. This may be due to the added factor (order), which could have reduced the power of the analysis as well as lowered the sensitivity.

6.5 Conclusion

When long-term memory performance is tested 90 min after encoding, moderate-intensity physical exercise intervention has been shown to yield greater enhancements compared to the high-intensity physical exercise intervention (Study 1) as well as passive rest (Study 3). However, it is important to note that the memory performance difference between moderate-intensity exercise and passive rest seen in Study 3, is not observed in Study 2. Reasons for this are discussed in Chapter 5.

Producing clear guidelines for memory enhancement that encompasses the variability in the literature can have major implications in the treatment of patients with memory deficiencies, provide a boost for students in exam and educational settings, as well as aid with daily tasks such as remembering items on a grocery list.

Chapter 3: The effects of transcranial direct current stimulation and physical exercise on long-term memory

1. Chapter Overview

Cognitive enhancement typically involves the amplification of core capacities of the mind through improvement of information processing systems (Bostrom & Sandberg, 2009; Looi & Cohen Kadosh, 2015). Research on cognitive enhancement strategies use interventions that target cognitive skills such as attention and memory. Generally, cognitive enhancement strategies include biochemical, physical, and behavioural interventions, such as pharmaceutical, electric stimulation, and physical exercise, respectively (Dresler et al., 2019). This chapter investigates the use of physical exercise and transcranial direct current stimulation (tDCS) as cognitive enhancement strategies to modulate memory.

While the literature has demonstrated positive effects on memory from both physical exercise (Loprinzi et al., 2019; Smith et al., 2010) and tDCS (Javadi & Walsh, 2012; Sandrini et al., 2016), their efficacy has not yet been compared and their combined effects yet to be studied. It is important to establish effective strategies for memory enhancement due to the far-reaching potential for applicability. For example, in the older population, enhanced memory – or a reduced rate of cognitive decline –, as a result of such strategies, could have major implications in the treatment of memory disorders such Alzheimer’s disease. This is especially true for tDCS given the physical constraints typically seen in the older population. Additionally, the link between physical exercise and enhanced memory, alongside a well-defined protocol, could encourage more of the population to participate in physical exercise and subsequently also improve their physical wellbeing.

The studies in this chapter aim to (a) compare the effects of physical exercise and tDCS on long-term memory, (b) determine whether a combination of the two interventions can elicit further memory modulation, and (c) determine the effects on memory performance after a 24h retention interval period. Based on the results from Chapter 2, the post-encoding moderate-intensity physical exercise protocol was selected for these studies. The tDCS protocol, adapted from previous research (Javadi & Walsh, 2012) was applied during encoding (reasons for this are explained in the introduction below). The same old-new recognition task employed in chapter 2 was also used here.

2. Introduction

The ambition to "stay ahead of the game" for the prospect of a successful career in today's modern-day society has been adding increasing pressure on individuals as the demands for cognitive functioning is ever-growing. The acquisition and maintenance of such skills requires time and effort through the expensive processes of education and training (Dresler et al., 2019). Obtaining such skills – or a lack thereof – has a significant impact on an individual and societal level (Dresler et al., 2019), and because the acquisition of these skills varies between individuals (for example, method and speed), the drive to gain more skills at a quicker pace has also increased. Subsequently, this has incentivised research into different strategies to enhance cognitive function beyond the norm.

In academic literature, cognitive enhancement commonly refers to enhanced performance on cognitive tasks (Dresler et al., 2019). Cognitive enhancement is generally associated with the use of drugs or medical devices/technologies that aim to enhance cognition via the augmentation of information processing systems (Bostrom & Sandberg, 2009; Dresler et al., 2019; Dubljević et al., 2015). As summarised by Dresler and colleagues

(2019), many cognitive enhancement strategies have been proposed in recent years and tend to fall under one of three categories: biochemical (e.g. pharmaceuticals, nutrition or natural remedies), physical (e.g. electric stimulation, and magnetic stimulation), and behavioural (e.g. physical exercise, sleep, and mnemonics). This introduction will focus on the memory-modulating capacity of electrical brain stimulation, specifically, non-invasive transcranial direct current stimulation (tDCS).

Brain stimulation was initially developed as a tool to treat psychiatric and neurologic disorders (e.g. Alzheimer’s disease, depression, and Parkinson’s disease). However, it has also demonstrated enhancing cognitive effects for the general/healthy population (Dresler et al., 2013). Brain stimulation can be achieved invasively or non-invasively, with the former able to attain superior target specificity via the placement of electrodes directly on- or inside the brain with the added accuracy of fMRI-guided positioning (Dresler et al., 2013).

During the past decade, tDCS application has seen a growing demand in both clinical studies as well as academic research. It has particularly been used as a non-invasive investigative tool in many memory studies for patients and healthy individuals, highlighting its importance as a means of modulating memory (Fregni et al., 2005; Javadi & Walsh, 2012; Looi & Cohen Kadosh, 2015; Reis et al., 2008; Wessel et al., 2015) (for review: Buch et al., 2017; Mancuso, Ilieva, Hamilton, & Farah, 2016). The use of tDCS has grown in popularity due to its low cost, ease of use, minimal adverse effects and portability (Carvalho et al., 2018). Furthermore, because tDCS has become increasingly user-friendly, home-based tDCS devices have been developed for patients to use from the leisure of their homes (Carvalho et al., 2018).

tDCS acts by influencing regions of the brain (rather than sending physiological signals) and inducing prolonged functional changes in the cerebral cortex via an electrical current applied on the scalp, usually 1 – 2 mA (Dresler et al., 2013; Javadi et al., 2012). In animal models, anodal cortical stimulation increased excitability for hours beyond the end of stimulation (Bindman et al., 1964; Nitsche & Paulus, 2001). Similarly, Nitsche and Paulus (2000) showed that 5 min of anodal tDCS in humans was enough to induce increases in cortical excitability for several minutes beyond the end of stimulation and indicated that the endurance of this effect is dependent on the intensity and duration of the stimulation (Nitsche & Paulus, 2000). A study by Nitsche and Paulus (2001) showed for the first time that a weak tDCS current is able to induce long-lasting increased cerebral excitability in humans that are dependent on the duration of tDCS stimulation. As previously discussed in Chapter 1, the mechanism by which tDCS exerts its effects are not well established, however, it likely induces an activation of voltage-gated presynaptic and postsynaptic sodium and calcium channels by subthreshold depolarisation (Nitsche & Paulus, 2001). Further, Nitsche and Paulus (2001) suggest that the activation of these channels could lead to increased presynaptic release of excitatory transmitters, as well as increased postsynaptic calcium influx, which is a known requirement for inducing lasting changes in synaptic efficiency (Nitsche & Paulus, 2001).

Studies using tDCS to modulate memory typically target the left dorsolateral prefrontal cortex (DLPFC) for stimulation as it has been shown to play a significant role in long-term memory formation by strengthening associations among items that are organised in working memory (Blumenfeld & Ranganath, 2006). Specifically, over half of tDCS studies target the F3 and F4 regions (10-20 International System for EEG placement); the regions where the left DLPFC is approximately located (Santarnecchi et al., 2015; Tremblay et al., 2014). Of these studies, over two-thirds target that region to investigate its effects on memory (Santarnecchi et al., 2015).

Several studies have demonstrated that tDCS over the left DLPFC during learning enhances recall of episodic memories in healthy individuals (Javadi & Walsh, 2012; Sandrini et al., 2016), as well as in patients suffering from stroke (Jo et al., 2009) or Parkinson's disease (Boggio et al., 2006). The aforementioned studies demonstrating enhanced memory performance after a bout of tDCS all used anodal tDCS. In contrast, cathodal tDCS has been shown to impair long-term memory (Javadi et al., 2012; Javadi & Walsh, 2012) as well as working memory (Boehringer et al., 2013; Zaehle et al., 2011). A study by Fregni and colleagues (2005) showed that anodal tDCS over the left DLPFC leads to enhanced working memory performance as demonstrated by increased accuracy of task performance relative to sham. The authors also highlight the effect of anodal tDCS is relatively focal and is polarity-dependent (Fregni et al., 2005). In a more recent study, Javadi and Walsh (2012) showed that if tDCS is administered over the left DLPFC during encoding or recognition, it can significantly enhance performance on a verbal memory task. Like Fregni and colleagues (2005), Javadi and Walsh also showed that the effects of anodal tDCS were relatively focal and polarity dependent (Javadi & Walsh, 2012). Collectively, this suggests that the use of tDCS brings about different behavioural effects that are both site specific (e.g. stimulation on DLPFC, cerebellum, posterior parietal cortex) and polarity dependent (use of anode or cathode electrode at stimulation site). However, it is important to note that paradoxical effects of tDCS have been reported by some studies (Hassanzahraee et al., 2020).

In addition to the effects of tDCS being site specific and polarity dependent, the literature suggests that stimulation duration, current amplitude, and timing of stimulation (onset) could also play a role in their efficacy. Ohn and colleagues (2008) found that anodal tDCS over the left DLPFC enhanced memory in a time-dependent manner. They found that by increasing stimulation to 30 min from 10 min, accuracy on a verbal memory task increased significantly

(Ohn et al., 2008). In another study (Elmer et al., 2009), 5 min of anodal tDCS over the left DLPFC did not produce any behavioural effects, however, Javadi and Walsh (2012) found that 1.6 s of anodal tDCS over the left DLPFC elicited enhanced performance on a word memorisation task if it is delivered during presentation of the stimuli (Javadi & Walsh, 2012).

Equally, current amplitude also plays a role on the efficacy of tDCS effects. Typically, memory studies employing tDCS use an amplitude of 1-2 mA. Whilst Boggio and colleagues (2006) and Hoy and colleagues (2014) tested the effects of tDCS on memory, they only found an effect at 2 mA (Boggio et al., 2006; Hoy et al., 2014a). However, significant effects on memory have been reported at 1.5 mA (Sandrini et al., 2016) as well as 1 mA (Ohn et al., 2008). This may suggest a non-linear relationship between amplitude and behavioural effects. Interestingly, however, looking at the data more closely, it is evident that current amplitude should be investigated in tandem with current density. Looking at current density (current strength divided by electrode size in cm^2) for these three studies, Ohn and colleagues (2008) had a current density of 40 µA/ cm^2 at 1 mA, whereas both Hoy and colleagues (2014) and Boggio and colleagues (2006) had a current density of 29 µA/ cm^2 at 1 mA. Accordingly, although all three studies employed a stimulation of 1 mA and for 20 min over the left DLPFC, the disparity lies within the current density, which could also play a role in the enhancing effects seen at 1 mA in the study by Ohn and colleagues (2008).

Finally, onset of tDCS relative to the memory task or recall/retrieval may also play a role on the effect on memory. Studies have shown enhanced memory when tDCS is applied before or during encoding (Hoy et al., 2014; Javadi & Walsh, 2012; Sandrini et al., 2016), and no significant effect when applied after encoding (Sahlem et al., 2015) or during recognition (Javadi & Walsh, 2012). Moreover, tDCS-induced changes in motor cortex excitability that led to enhanced performance of a reaction time task have been shown to be critically dependent on the time interval between stimulation and task performance (Molero-Chamizo et al., 2018). Interestingly, a study by Javadi, Cheng and Walsh (2012), tested the effects of short duration tDCS (1.6 s) applied during word presentation or immediately after (but still during the cognitive task) and found that tDCS applied during word presentation led to significantly better memory performance than when applied after word presentation, further highlighting the importance of the timing of tDCS onset (Javadi et al., 2012).

In sum, the literature demonstrates varying degrees of tDCS-induced memory modulation and provides evidence for several key modulators: duration of stimulation, site specificity, polarity, amplitude as well as onset of stimulation relative to encoding. Broadly, anodal tDCS over the left DLPFC tends to enhance memory, whereas cathodal tDCS impairs it (Javadi & Walsh, 2012).

3. Hypotheses

3.1 Study 4

In this study, the effects of tDCS were compared to moderate-intensity physical exercise and rest (control).

H1: There will be no observable difference in performance score on the old/new recognition task between physical exercise and tDCS.

H2: Physical exercise will yield a higher performance score on the old/new recognition task than rest (control).

H3: tDCS will yield a higher performance score on the old/new recognition task than rest (control).

3.2 Study 5

In this study, the effects of moderate-intensity physical exercise were compared to a combined intervention (exercise and tDCS) and rest (control) following a 90 min retention interval.

H1: Physical exercise will yield a higher performance score on the old/new recognition task than rest (control).

H2: The combined intervention will have a higher performance score on the old/new recognition task compared to the physical exercise intervention.

H3: The combined intervention will yield a higher performance score on the old/new recognition task than rest (control).

3.3 Study 6

In this study, the effects of moderate-intensity physical exercise were compared to a combined intervention (exercise and tDCS) and rest (control) following a 24h retention interval.

H1: Physical exercise will yield a comparable performance score on the old/new recognition task compared to rest (control).

H2: The combined intervention will yield a higher performance score on the old/new recognition task compared to the exercise intervention.

H3: The combined intervention will yield a comparable performance score on the old/new recognition task compared to rest (control).

4. Methods

4.1 Study 4

4.1.1 Participants.

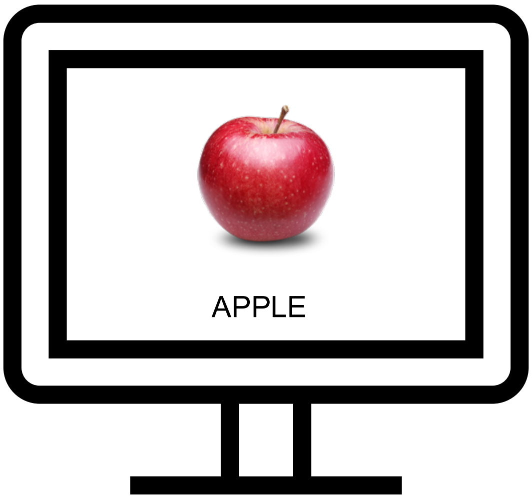
A total of 20 participants (6 males; M_{age} = 22.57, *SD* = 2.91) took part in this study. All participants were undergraduate psychology students attending the University of Kent and were recruited via the Research Participation Scheme (RPS). All participants were right-handed with no previous mental illness/disorder and were non-smokers to light smokers. Participants were native speakers in either English, German, French or Spanish. Each participant attended three sessions, at least five days apart from one another. Details of the study were explained and information regarding potential risk factors of participating in a study involving physical exercise was given. The order of the three sessions was randomised. All participants signed consent forms in accordance with the Declaration of Helsinki and approved by the ethical committee of the University of Kent. Additionally, all participants completed as Physical Activity Readiness Questionnaire (PARQ) to ensure suitability for the physical activity involved in the study. At the end of the study, participants were awarded RPS credits for their participation.

4.1.2 Materials.

A bank of 480 neutral emotional images were used as stimuli for the old/new recognition task. These images consisted of objects, animals, and food. None of the images contained any people/faces. Stimuli were selected from two databases (Bank of Standardised Stimuli, and MIT Objects Stimuli) as well as from Google Image Search with an emphasis on neutral valence. Stimuli were presented on Matlab on a Windows PC. Each image was displayed on screen for 1 s with its name displayed below the image (Figure 11), followed by a fixation cross for 1 s to transition to the next image. Coding for the learning and recall tasks on Matlab and PsychToolbox were created by Dr Amir-Homayoun Javadi. Heart rate was monitored using a Mio Technology Mio Fuse Heart Rate Monitor. Physical exercise, in the form of cycling, was performed on a Stages Cycling SC3 cycle ergometer with a built-in power meter and display console. Direct electrical current was delivered using a NeuroConnDC Brain Stimulator Plus unit (Rogue Resolutions, Wales, UK).

Figure 11.

On-screen stimuli presentation



4.1.3 Procedure.

Study 4 followed a within-subjects design consisting of three conditions. For an overview of the study procedure, refer to *Figure 12 (a).*

4.1.3.1 Learning and recall phase.

During the learning phase, participants were shown a set of 70 images of which they had to memorise. The images were presented in two blocks of 35 images with 1 min break between each block. A fixation cross appeared for 1s between each image. Participants were instructed to memorise the concept of the image rather than the image itself, as in the recall phase they were shown either an identical image or a similar image with a different shape, colour, or orientation (*Figure 13*).

During the recall phase, participants were shown 140 images. 70 of these images were either already presented during the learning phase, or a similar image was shown that represented the same concept, e.g. a red bottle shown in training phase, and a blue bottle shown in recall phase (concept of image – a bottle – remained the same). The remaining 70 images were new images that were not seen during the learning phase. Similar to the learning phase, the images were presented in two blocks with a 1 min break in between each block. Their task during the recall phase was to identify which of the images were old or new using the left and right arrow keys on the keyboard. Each session contained different images to avoid any memory overlap.

4.1.3.2 Physical exercise.

In this study, physical exercise was preceded by a period of sham transcranial direct current stimulation (tDCS). The physical exercise task consisted of 30 min cycling on a cycle ergometer and was split into seven blocks. Participants started with a 2 min warm up block followed by a 1 min break. The next six blocks consisted of 4 min cycling followed by a 1 min break. Each block had a different cadence that the participant had to maintain. Cadences of each block were randomised. At the beginning of each of these six blocks participants were informed of the cadence for that block and were asked to maintain and monitor their cadence on the cycle display. During cycling, the resistance on the cycle ergometer was adjusted and controlled by the experimenter to maintain the participants' heart rate within 60-

70% of maximum (HR_{max}). HR_{max} was calculated using the formula obtained from Tanaka et al. (2001): $HR_{max} = 208 – (0.7 * age)$. After each block, participants were asked to give their RPE score using the Borg Scale (Borg, 1982). Participants reporting an RPE score below 12 or more than 16 on the Borg Scale for two or more blocks were excluded (n = 0).

4.1.3.3 Transcranial direct current stimulation.

To accurately place the anode electrode onto the scalp of each participant, head measurements were taken and the region representing the left dorsolateral prefrontal cortex (DLPFC) was marked (F3 location in accordance with the 10-20 international system for EEG placement). The area of stimulation was cleaned using a skin preparation gel. Transcranial direct current stimulation (tDCS) was administered via a surface sponge electrode (50 x 70 mm) soaked in saline solution. The reference (cathode) electrode was placed on the outer side of the wrist on the left hand. The electrodes were secured in position using a self-adhesive bandage and bandage clips. A direct current of 1.5 mA with a fade-in and fade-out time of 10s was delivered for 5 min prior to the start of encoding and continued until the end of the learning phase. For the sessions using sham stimulation, all procedures from the active stimulation sessions were replicated with the only difference being that the experimenter turned off the stimulation after 10s without the participants' knowledge, thus keeping the participant blind to the session type. As a safety measure, this button press was replicated during active stimulation after 10s, but in this case stimulation was not cancelled. For details of when active/sham stimulation was administered please refer to the detailed schematic (Figure 12).

4.1.3.4 Rest and retention interval.

For the non-exercise sessions, cycling was replaced with 30 min of rest (active wakeful rest). During this rest phase participants watched 30 min of “Friends” (TV show). For all sessions, after rest or cycling phase, participants entered a controlled retention period lasting 90 min, during which the Friends TV show was played.

4.1.4 Statistical analysis.

Data analysis was performed using SPSS (v19; LEAD Technologies, Inc, Charlotte, NC). Accuracy for the recognition of the old and new image word pairs were analysed separately. Using signal detection theory, d' values are also reported. One-way repeated measures of analysis of variance (rANOVA) was used to investigate the main effect of condition with per- centage accuracy in recognition and reaction time for the old and new image word pairs. Significant threshold of $p < 0.05$ was chosen. Following significant main effect of condition, post-hoc paired-sample t-tests were run to investigate the difference between groups. False discovery rate (FDR) was used for correction for multiple comparisons for post-hoc tests. Participants who have scored less than 55% on the old/new recognition were excluded from analysis (n = 0).

4.2 Study 5

4.2.1 Participants.

A total of 18 participants (4 males; $M_{age} = 19.39$, $SD = 0.70$) took part in Study 5. All participants were undergraduate psychology students attending the University of Kent and were recruited via the Research Participation Scheme (RPS). All participants were right-handed with no previous mental illness/disorder and were non-smokers to light smokers.

Participants were native speakers in either English, German, French or Spanish. Each participant attended three sessions, at least five days apart from one another. Details of the study were explained and information regarding potential risk factors of participating in a study involving physical exercise was given. The order of the three sessions was randomised. All participants signed consent forms in accordance with the Declaration of Helsinki and approved by the ethical committee of the University of Kent. Additionally, all participants completed as Physical Activity Readiness Questionnaire (PARQ) to ensure suitability for the physical activity involved in the study. At the end of the study, participants were awarded RPS credits for their participation.

4.2.2 Materials.

Identical to Study 4. Please refer to section 4.1.2.

4.2.3 Procedure.

Study 5 followed a within-subjects design consisting of three conditions. For an overview of the study procedure, refer to *Figure 12 (b).*

4.2.3.1 Learning and recall phase.

Procedures were performed in the same manner as Study 4, however, in this study participants were shown a set of 80 images during the learning phase and 160 images in the recall phase.

4.2.3.2 Physical exercise.

In this study, there were two physical exercise sessions. Each of which was preceded by either sham- or active-tDCS. The physical exercise protocol used in Study 4 was used in this study. Participants reporting an RPE score below 12 or more than 16 on the Borg Scale for two or more blocks were excluded (n = 1).

4.2.3.3 Transcranial direct current stimulation.

Identical to Study 4, with the exception that a direct current of 1.5 mA with a fade-in and fade-out time of 10 s was delivered for 5 min prior to the start of encoding.

4.2.3.4 Rest and retention interval.

Identical to Study 4. Please refer to section 4.1.3.4.

4.2.4 Statistical analysis.

Data analysis was performed using SPSS (v19; LEAD Technologies, Inc, Charlotte, NC). Accuracy for the recognition of the old and new image word pairs were analysed separately. Using signal detection theory, d' values are also reported. One-way repeated measures of analysis of variance (rANOVA) was used to investigate the main effect of condition with percentage accuracy in recognition and reaction time for the old and new image word pairs. Significant threshold of $p < 0.05$ was chosen. Following significant main effect of condition, post-hoc paired-sample t-tests were run to investigate the difference between groups. False discovery rate (FDR) was used for correction for multiple comparisons for post-hoc tests. Participants who have scored less than 55% on the old/new recognition were excluded from analysis (n = 0).

4.3 Study 6

4.3.1 Participants.

A total of 84 participants (Active tDCS + PE: n = 28, M_{age} = 18.64, *SD* = 0.70; Sham tDCS + PE: 6 male, n = 28, M_{age} = 19.69, *SD* = 2.70; Sham tDCS + Rest: 1 male, n = 28, M_{age} = 18.91, *SD* = 3.96) took part in Study 6. All participants were undergraduate psychology students attending the University of Kent and were recruited via the Research Participation Scheme (RPS). All participants were right-handed with no previous mental illness/disorder and were non-smokers to light smokers. Participants were native speakers in either English, German, French or Spanish. Each participant attended three sessions, at least five days apart from one another. Details of the study were explained and information regarding potential risk factors of participating in a study involving physical exercise was given. Participants were randomly allocated to an intervention. All participants signed consent forms in accordance with the Declaration of Helsinki and approved by the ethical committee of the University of Kent. Additionally, all participants completed as Physical Activity Readiness Questionnaire (PARQ) to ensure suitability for the physical activity involved in the study. At the end of the study, participants were awarded RPS credits for their participation.

4.3.2 Materials.

Identical to Study 4 and 5. Please refer to section 4.1.2.

4.3.3 Procedure.

Due to a change in RPS credit scheme, which limited the number of maximum credits allowed to be rewarded per study, Study 6 had to change to a between-subjects design.

Participants were allocated to only one of the three conditions. For an overview of the study procedure, refer to *Figure 12 (c).*

4.3.3.1 Learning and recall phase.

Procedures were performed in the same manner as Study 5. Please refer to section 4.2.3.1.

4.3.3.2 Physical exercise.

In this study, there were two physical exercise sessions. Each of which was preceded by either sham- or active-tDCS. The physical exercise protocol used in Study 5 was used in this study. Participants reporting an RPE score below 12 or more than 16 on the Borg Scale for two or more blocks were excluded (n = 3).

4.3.3.3 Transcranial direct current stimulation.

Identical to Study 5. Please refer to section 4.2.3.3.

4.3.3.4 Rest and retention interval.

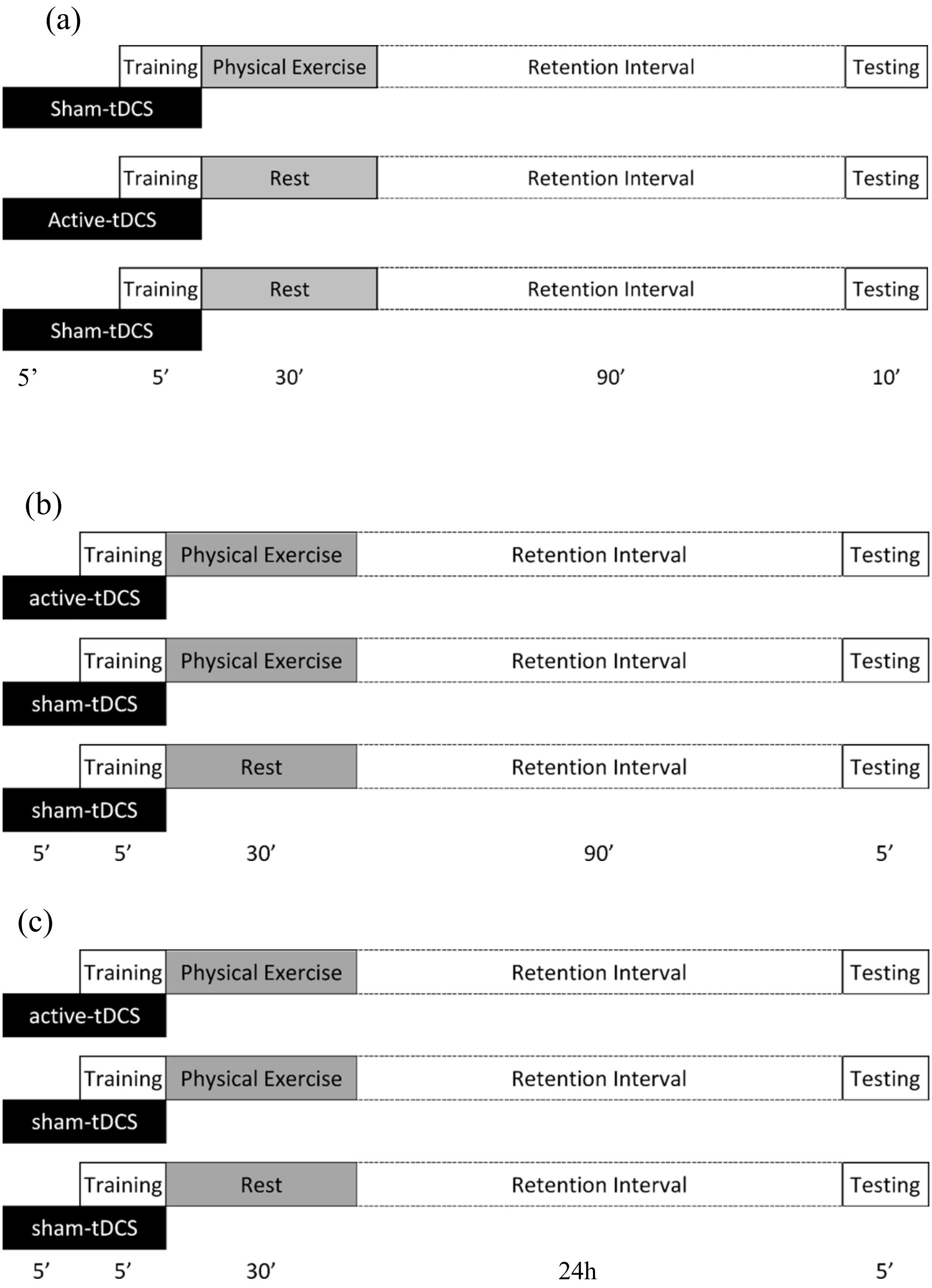
Identical to Study 5, with the exception that the retention interval lasted 24h.

4.3.4 Statistical analysis.

Data analysis was performed using SPSS (v19; LEAD Technologies, Inc, Charlotte, NC). Accuracy for the recognition of the old and new image word pairs were analysed separately. Using signal detection theory, d' values are also reported. One-way repeated measures of analysis of variance (rANOVA) was used to investigate the main effect of condition with per- centage accuracy in recognition and reaction time for the old and new image word pairs. Significant threshold of $p < 0.05$ was chosen. Following significant main effect of condition, post-hoc paired-sample t-tests were run to investigate the difference between groups. False discovery rate (FDR) was used for correction for multiple comparisons for post-hoc tests. Participants who have scored less than 55% on the old/new recognition were excluded from analysis (n = 2).

Figure 12.

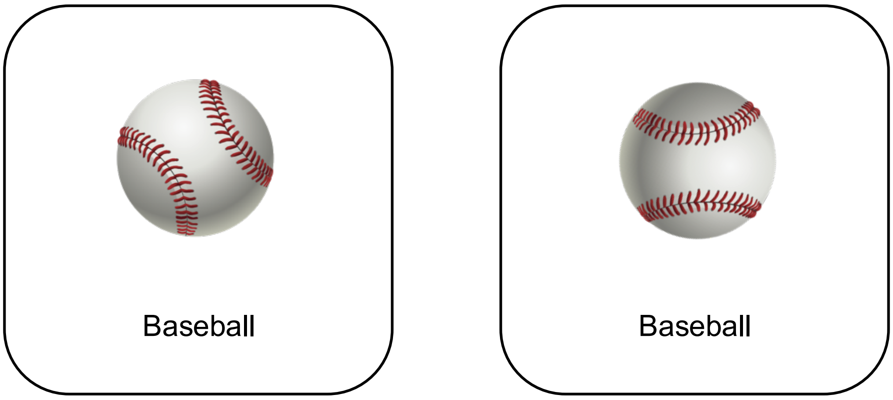
Schematic of all procedures



Note: (a) Study 4 procedure. Participants attended 3 sessions: physical exercise, active tDCS, and sham-tDCS (control). Duration of each phase, in minutes, is indicated below the diagram. (b) Study 5 procedure. Participants attended 3 sessions: physical exercise + active tDCS, physical exercise + sham tDCS, and rest + sham tDCS (control). (c) Study 6 procedure. Participants attended 3 sessions: physical exercise + active tDCS, physical exercise + sham tDCS, and rest + sham tDCS (control). Time (at the bottom of each schematic) is measured in minutes unless otherwise stated.

Figure 13.

Sample of how the stimuli appeared during the learning phase and recall phase.



Note: The images represent how the two stimuli represent the same concept (in this case, a baseball) but can differ in orientation, colour, or shape.

5. Results

Table 7 summarises the descriptive statistics for all three studies. Table 8 summarises the rANOVA for studies 4 and 5 and ANOVA for study 6 separated by old and new images, performance accuracy, and reaction time. Table 7 summarises the post-hoc comparisons for old images between different intervention conditions. Figure 14 shows performance accuracy scores for all three studies across the different interventions. Figure 15 shows reaction time scores for all three studies across the different interventions.

Order effect analysis was also run (Table 10). No pattern in favour of one intervention order over another was observed for studies 4 and 5 ($p > 0.05$). Power output data including mean heart rate is summarised in Table 11.

5.1 Study 4

Analysis revealed a statistically significant effect on performance accuracy scores of old images, $F(2,34) = 4.984$, $p = 0.013$, $\eta_p^2 = 0.227$. No statistically significant effects were observed for reaction time, $F(2,34) = 0.303$, $p = 0.741$, $\eta_p^2 = 0.018$.

A paired sample t-test was run on a sample of 18 participants to determine whether there was a statistically significant mean difference between performance accuracy scores between each intervention. The physical exercise intervention produced a higher mean score (87.853) as opposed to the rest intervention (74.298); a statistically significant increase of 13.555 (95% CI, 2.625 to -26.486), $t(17) = 2.574$, $p = 0.02$, $d = 0.607$. This sample size enabled me to achieve > 0.4 power at two-tailed $\alpha = 0.05$.

The physical exercise intervention produced a higher mean score (87.853) as opposed to the tDCS intervention (85.952); a statistically insignificant increase of 1.901 (95% CI, -4.745 to -8.547), $t(17) = 0.603$, $p = 0.554$, $d = 0.142$.

The tDCS intervention produced a higher mean score (85.952) as opposed to the rest intervention (74.298); a statistically significant increase of 11.654 (95% CI, 0.451 to -24.858), $t(17) = 2.188$, $p = 0.043$, $d = 0.516$. However, re-running the analysis using d' altered the results for post-hoc comparisons between tDCS and rest ($p = 0.082$, $d = 0.435$).

5.2 Study 5

Analysis revealed a statistically significant effect on performance accuracy of old images, F(2,34) = 7.739, p = 0.002, $\eta_p^2 = 0.313$. No statistically significant effects were observed for reaction time, F(2,34) = 0.393, p = 0.678, $\eta_p^2 = 0.023$.

A paired sample t-test was run on a sample of 18 participants to determine whether there was a statistically significant mean difference between performance accuracy scores between each intervention. The physical exercise intervention produced a higher mean score (69.722) as opposed to the rest intervention (61.389); a statistically significant increase 8.333 (95% CI, 2.660 to -14.006), *t*(17) = 4.099, *p* = 0.007, *d* = 0.730. This sample size enabled me to achieve > 0.56 power to detect an effect size of Cohen's *d* = 0.730 at two-tailed α = 0.05.

The physical exercise intervention produced a higher mean score (69.722) as opposed to the combined intervention (64.167); a statistically significant increase 5.555 (95% CI, -8.867 to -2.244), *t*(17) = 4.540, *p* = 0.003, *d* = 0.834. This sample size enabled me to achieve > 0.68 power at two-tailed α = 0.05.

The combined intervention produced a higher mean score (64.167) as opposed to the rest intervention (61.389); a statistically insignificant increase 2.778 (95% CI, -1.579 to -7.135), *t*(17) = 1.345, *p* = 0.196, *d* = 0.317. Re-running the analysis using d' did not alter the results.

5.3 Study 6

Analysis revealed a statistically significant effect on performance accuracy of old images, F(2,81) = 3.319, p = 0.041, ηp2 = 0.076. No statistically significant effects were observed for reaction time, F(2,81) = 0.938, p = 0..396, ηp2 = 0.023.

An independent t-test was run on a sample of 84 participants to determine whether there was a statistically significant mean difference between performance accuracy scores between each intervention. The physical exercise intervention produced a lower mean score (57.768) as opposed to the rest intervention (62.277); a statistically insignificant decrease of 4.509 (95% CI, -12.378 to -4.360), $t(54) = 1.149$, $p = 0.256$, $d = 0.313$.

The combined intervention produced a lower mean score (51.884) as opposed to the rest intervention (62.277); a statistically significant decrease of 10.393 (95% CI, -18.414 to -2.372), $t(54) = 2.598$, $p = 0.012$, $d = 0.707$. This sample size enabled me to achieve > 0.74 power to detect an effect size of Cohen's $d = 0.707$ at two-tailed $\alpha = 0.05$.

The combined intervention produced a lower mean score (51.884) as opposed to the physical exercise intervention (57.768); a statistically insignificant decrease of 5.884 (95% CI, -14.317 to -2.549), $t(54) = 1.399$, $p = 0.168$, $d = 0.381$. However, re-running the analysis using d' altered the results for post-hoc comparisons between the combined intervention and physical exercise intervention (p = 0.048, d = 0.55). This sample size enabled me to achieve > 0.52 power at two-tailed $\alpha = 0.05$.

Table 7.

Summary of descriptive statistics for studies 4 – 6.

Study	**Measure**	**Condition**	**Old images**	**New images**	**d’**
Study 4	Accuracy	Exercise	87.853[8.722]	93.534[6.821]	3.150[0.817]
		tDCS	85.952[14.510]	93.968[4.913]	3.028[1.007]
		Rest	74.298[27.625]	94.179[7.634]	2.588[0.886]
	RT	Exercise	1.435[0.818]	1.639[0.739]	
		tDCS	1.336[0.825]	1.960[1.796]	
		Rest	1.505[0.878]	1.466[0.539]	
Study 5	Accuracy	PE + tDCS	64.167[18.481]	82.639[12.587]	1.551[0.907]
		Exercise	69.722[17.228]	84.167[12.827]	1.915[1.248]
		Rest	61.389[18.820]	84.333[12.697]	1.472[0.968]
	RT	PE + tDCS	1.097[0.193]	1.158[0.211]	
		Exercise	1.146[0.306]	1.276[0.389]	
		Rest	1.118[0.268]	1.248[0.296]	
Study 6	Accuracy	PE + tDCS	51.884[16.004]	79.641[11.082]	0.957[0.378]
		Exercise	57.768[15.469]	81.295[11.963]	1.174[0.425]
		Rest	62.277[14.857]	80.938[9.407]	1.278[0.477]
	RT	PE + tDCS	1.432[0.911]	1.215[0.347]	
		Exercise	1.282[0.227]	1.262[0.361]	
		Rest	1.233[0.292]	1.320[0.555]	

Notes: (mean [SD]) split over old images and new images. RT: reaction time. Exercise: moderate-intensity physical exercise intervention. PE + tDCS: a combination of tDCS and physical exercise.

Table 8.

Summary of rANOVA for studies 4 – 5 and ANOVA for study 6 separated by old images and new images, performance accuracy and reaction time.

		Old images			New images		
Experiment	Measure	F	p	η_p^2	F	p	η_p^2
Study 4	Accuracy	F(2,34)=4.984	0.013	0.227	F(2,34)=0.092	0.912	0.005
	RT	F(2,34)=0.303	0.741	0.018	F(2,34)=1.494	0.239	0.081
Study 5	Accuracy	F(2,34)=7.739	0.002	0.313	F(2,34)=0.312	0.734	0.018
	RT	F(2,34)=0.393	0.678	0.023	F(2,34)=1.710	0.196	0.091
Study 6	Accuracy	F(2,81)=3.319	0.041	0.076	F(2,81)=0.180	0.836	0.004
	RT	F(2,81)=0.938	0.396	0.023	F(2,81)=0.421	0.658	0.010

Table 9.

Summary of the post-hoc paired-sample t-tests for studies 4 – 5 and independent t-test for study 6.

Study	**Measure**	**Comparison**	**t**	**p**	**d**	**95% CI**
Study 4	Accuracy	Exercise vs tDCS	t(17) = 0.603	0.554	0.142	-4.745 – 8.547
		Exercise vs Rest	t(17) = 2.574	0.020	0.607	2.625 – 26.486
		tDCS vs Rest	t(17) = 2.188	0.043	0.516	0.451 – 24.858
	RT	Exercise vs tDCS	t(17) = 0.624	0.541	0.147	-0.236 – 0.435
		Exercise vs Rest	t(17) = 0.288	0.777	0.068	-0.577 – 0.438
		tDCS vs Rest	t(17) = 0.694	0.497	0.164	-0.680 – 0.343
	d'	Exercise vs tDCS	t(17) = 0.431	0.672	0.102	-0.473 – 0.716
		Exercise vs Rest	t(17) = 4.932	0.000	1.162	0.322 – 0.802
		tDCS vs Rest	t(17) = 1.847	0.082	0.435	-0.063 – 0.944

Study 5	Accuracy	PE + tDCS vs Exercise	t(17) = 4.540	0.003	0.834	-8.867 – -2.244
		PE + tDCS vs Rest	t(17) = 1.345	0.196	0.317	-1.579 – 7.135
		Exercise vs Rest	t(17) = 4.099	0.007	0.730	2.660 – 14.006
	RT	PE + tDCS vs Exercise	t(17) = 0.867	0.398	0.204	-0.169 – 0.070
		PE + tDCS vs Rest	t(17) = 0.351	0.730	0.083	-0.146 – 0.105
		Exercise vs Rest	t(17) = 0.561	0.582	0.132	-0.078 – 0.134
	d'	PE + tDCS vs Exercise	t(17) = 4.042	0.007	0.717	-0.616 – -0.112
		PE + tDCS vs Rest	t(17) = 0.807	0.431	0.190	-0.126 – 0.283
		Exercise vs Rest	t(17) = 2.989	0.008	0.705	0.130 – 0.754
Study 6	Accuracy	PE + tDCS vs Exercise	t(54) = 1.399	0.168	0.381	-14.317 – 2.549
		PE + tDCS vs Rest	t(54) = 2.598	0.012	0.707	-18.414 – -2.372
		Exercise vs Rest	t(54) = 1.149	0.256	0.313	-12.378 – 4.360
	RT	PE + tDCS vs Exercise	t(54) = 0.848	0.400	0.231	-0.205 – 0.506
		PE + tDCS vs Rest	t(54) = 1.103	0.275	0.300	-0.163 – 0.562
		Exercise vs Rest	t(54) = 0.699	0.488	0.190	-0.091 – 0.189
	d'	PE + tDCS vs Exercise	t(54) = 2.023	0.048	0.551	-0.433 – -0.002
		PE + tDCS vs Rest	t(54) = 2.794	0.007	0.760	-0.552 – -0.091
		Exercise vs Rest	t(54) = 0.861	0.393	0.234	-0.346 – 0.138

Note: Accuracy: performance accuracy. RT: reaction time. 95% CI: confidence interval. d: Cohen’s d. d’: D prime

Table 10.

Order effect analysis for studies 4 and 5.

Study	**Effect**	**F**	**p**	η_p^2
Study 4	Intervention	F(2,32)=3.657	0.037	0.186
	Order	F(1,16)=1.285	0.274	0.074
	Intervention × Order	F(2,32)=1.195	0.316	0.069
Study 5	Intervention	F(2,32)=1.229	0.306	0.071
	Order	F(1,16)=0.819	0.379	0.049
	Intervention × Order	F(2,32)=0.006	0.994	0.000

Table 11.

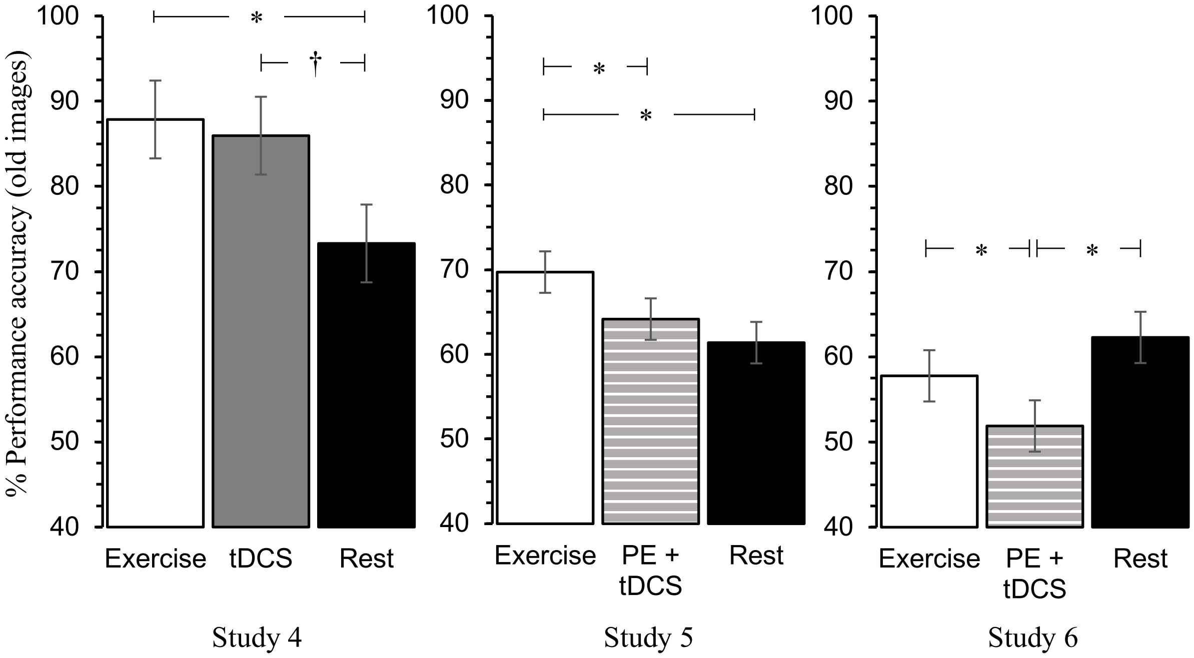
Summary of mean heart rate, power and energy for studies 5 – 6.

Study	Intervention	Heart rate (BPM)	Power (Watts)	Energy (Joules)
Study 5	Moderate Intensity PE	113.16 (6.61)	41.76 (21.08)	60138.95 (30354.42)
	Combined Intervention	109.42 (8.55)	41.00 (14.70)	59040.00 (21169.03)
Study 6	Moderate Intensity PE	106.48 (14.51)	36.51 (12.25)	52571.08 (17640.23)

Note: All values are mean (SD) of median measurements. Measurements occurred once every second (1 Hz). No data was recorded for Study 4 or the combined intervention for Study 6.

Figure 14.

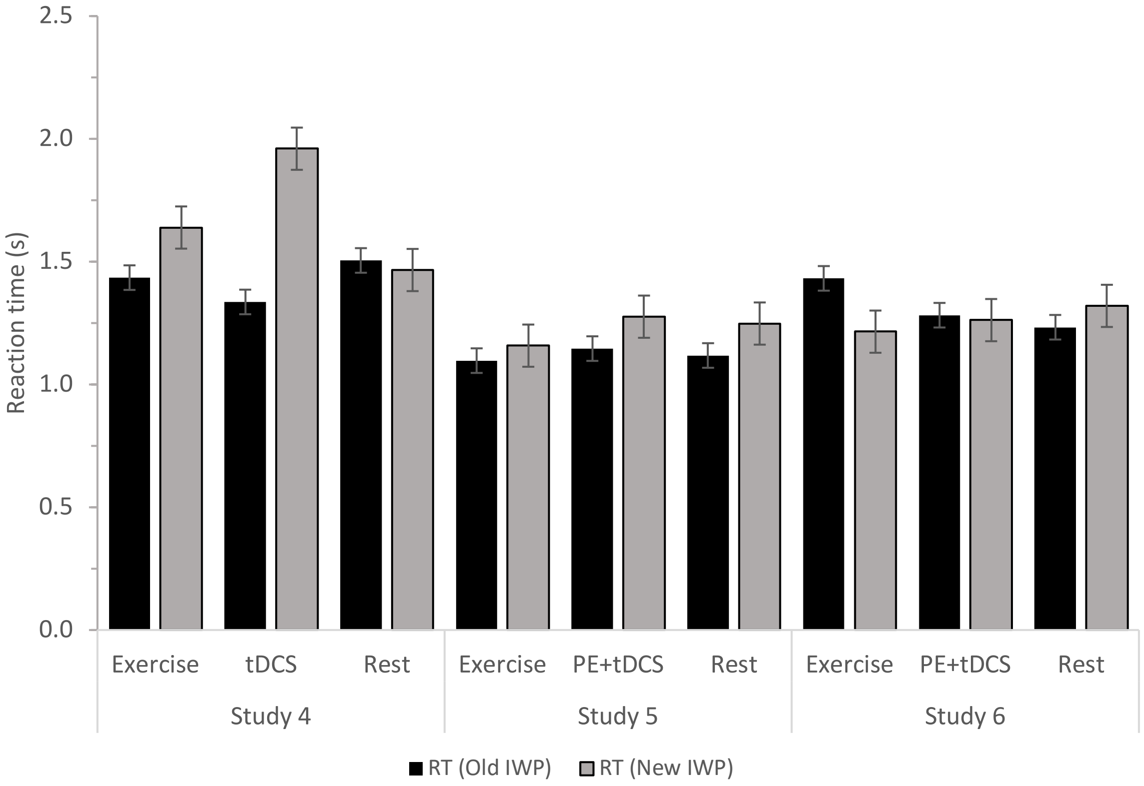
Performance accuracy scores for studies 4 – 6 across the different interventions.



Note: *p<0.020 significance corrected for multiple comparisons using false discovery rate (FDR). † p = 0.043. Error bars represent one standard error of the mean.

Figure 15.

Reaction time scores for studies 4 – 6 across the different interventions.



Note: Error bars represent one standard error of the mean.

6. Summary

The aims of this chapter were to (a) compare the effects of physical exercise and tDCS on long-term memory performance, (b) determine whether a combination of these two interventions would elicit further memory modulation, and (c) determine the effects physical exercise, the combined intervention, and rest on memory performance after a 24h retention interval. To investigate these aims, three studies were run where memory performance was assessed using an old/new recognition task.

6.1 Study 4

This study compared the modulatory effects of tDCS, physical exercise, and rest (control) on long-term memory. Performance accuracy was assessed using an old/new recognition task that was employed 90 min after learning.

The results suggested that physical exercise, performed at a moderate intensity, significantly enhanced memory performance compared to rest. This falls in line with several studies showing enhanced long-term memory performance after a bout of moderate intensity physical exercise (Coles & Tomporowski, 2008; Pesce et al., 2009). The results also showed that 15 min of anodal tDCS over the left DLPFC did not enhance memory performance compared to rest . Whilst this result achieved significance ($p = 0.043$), statistical confidence has been adjusted to $p < 0.020$ to correct for multiple comparisons using FDR. Finally, no significant difference in memory performance was observed between physical exercise and tDCS, suggesting that their effect on long-term memory performance is comparable. These results support the original hypotheses.

6.2 Study 5

This study compared the modulatory effects of physical exercise, rest (control), and a combined intervention of physical exercise and tDCS on long-term memory. Performance accuracy was assessed using an old/new recognition task that was employed 90 min after learning.

The results showed that, like in Study 4, physical exercise elicited significantly greater enhancements to long-term memory performance than rest on the old/new recognition task. Interestingly, the combined intervention of physical exercise and tDCS was significantly worse than physical exercise on its own, which is in contrast to the original hypothesis.

Initial predictions for this result could be that the mechanisms involved in facilitating tDCS-induced memory enhancement may actively compete for the same neural resources required by the mechanisms that facilitate physical-exercise-induced memory enhancements. Consequently, this leads to diminished activation of both memory-enhancing mechanisms. This can be incidentally compared to the competitive agonist-antagonist relationship between drug molecules competitively trying to bind on receptors at the same binding site.

On the other hand, the diminished memory performance of the combined intervention may be a result of homeostatic measures, similar to those described by the Bienenstock-Cooper-Munro rule (Bienenstock et al., 1982), which prevent excessive brain activation as a result of over-excitation by reversing the excitatory effects.

More on these theories will be discussed in the general discussion (chapter 5).

6.3 Study 6

This study compared the modulatory effects of physical exercise, rest (control), and a combined intervention of physical exercise and tDCS on long-term memory. Performance accuracy was assessed using an old/new recognition task that was employed 24h after learning.

By increasing the retention interval to 24h, the effects of physical exercise on long-term memory performance were no longer significantly better than rest. This supports the original hypothesis, which predicted that physical exercise would yield a comparable performance score on the old/new recognition task compared to rest. The rationalisation behind this hypothesis is three-fold: a) the effects of rest on long-term memory over longer periods of time, b) the effects of sleep (which are evidently introduced given the 24h retention period), and c) the chosen physical exercise intensity for the study.

Dewar and colleagues (2012) found that wakeful rest significantly enhanced memory performance 15-30 min and 7 days after encoding compared to a spot-the-difference game. This was especially evident after 7 days, where the authors suggested that the memory enhancement effects persisted throughout rather than being diluted over time. It was also confirmed that this was not a result of retrieval interference from the distractor task as both conditions were followed by a spot-the-difference game (Dewar et al., 2012).

Although in both sleep and passive wakeful rest, acetylcholine levels are significantly reduced compared to active wakefulness (thought to promote hippocampal-cortical communication that aids memory consolidation) (Wamsley, 2019), sleep has repeatedly been shown to enhance long-term memory to a greater extent than that of wakeful rest (for review: Stickgold, 2005).

Lastly, studies have shown time-dependent effects of physical exercise intensity on memory performance (Coles & Tomporowski, 2008; Hötting et al., 2016). For example, Hötting and colleagues (2016) compared submaximal and maximal intensities of physical exercise on memory performance and found that only the participants in the maximal intensity group forgot less words than control (rest) when memory was tested after 24h.

Therefore, given the moderate intensity physical exercise protocol employed in this study, and factoring in the effects of sleep and the effects of rest over a longer retention interval, it was hypothesised that moderate-intensity physical exercise would yield comparable performance scores on the old/new recognition task.

The results also showed that the combined intervention (exercise + tDCS) performed significantly worse than both the physical exercise intervention on its own and rest/control, suggesting memory impairment. These results do not support the original hypotheses. Following the aforementioned rationalisation, it was originally predicted that the combined intervention would yield a higher performance score compared to physical exercise and rest. In the most straightforward line of thinking, this was hypothesised because both tDCS and physical exercise have been shown to enhance memory performance as independent interventions, and therefore, it was assumed that a combination of both interventions would further enhance memory performance. As to why the combined intervention performed worse than physical exercise alone, it is plausible that the negative effects mentioned in section 6.2 (above) are intensified following a longer retention interval. Further, it is important to reiterate the 24h retention interval here because the effects of passive wakeful rest on long-term memory performance could have been facilitated by sleep.

6.4 Considerations

There was some degree of variability to performance accuracy scores for the physical exercise interventions across the three studies. This may be due to differences in the duration of retention interval, individual differences in response to physical exercise, differences in baseline cognitive abilities and motivation to complete the tasks (Katz et al., 2017). This highlights the need to account for other modulating factors such as fitness level, general cognitive abilities, and motivation. Additionally, further participant screening, such as screening for anxiety or habitual physical activity, may provide a deeper understanding of how emotional states or fitness levels can influence how physical exercise modulates long-term memory.

With regards to the order effect analysis, study 5 has come up as non-significant for intervention effect, as opposed to significant before this analysis was run. This may be due to the added factor (order), which could have reduced the power of the analysis as well as lowered the sensitivity.

6.5 Conclusion

The studies in this chapter have shown that a mild regimen of physical exercise can enhance long-term memory. However, it may be that higher intensities of physical exercise are required to induce longer periods of retention (e.g. enhanced retention for 7 days). Furthermore, tDCS over the left DLPFC has been shown to enhance memory on par with physical exercise. Lastly, whilst tDCS and physical exercise can enhance long-term memory as two independent interventions, it is clear that combining them has the opposite effect. Put simply, too much of a good thing can be bad.

Chapter 4: Neural oscillatory activity during physical exercise

1. Chapter Overview

Research on memory modulation investigates the neurobiological processes and systems that underlie the differences in memory strength (Roozendaal & McGaugh, 2011). Distinct modulatory systems affect specific neurological processes that are fundamental to memory consolidation and recall. Brain oscillations, considered to be a core neural mechanism for long-term memory storage and retrieval, can be recorded in real-time to provide a better understanding of how oscillatory dynamics across the frequency band are linked to memory (Hanslmayer et al., 2012; Sauseng & Klimesch, 2008).

Numerous studies have examined the effects of physical exercise on memory (for review: Chang, Labban, Gapin, & Etnier, 2012; Loprinzi, Edwards, & Frith, 2017; Smith et al., 2010). Moreover, several studies have used EEG to record the effects of exercise on brain activity (Cheron et al., 2016; Ciria et al., 2018). However, investigation of the modulatory effects of physical exercise on brain activity during the exercise task in relation to long-term memory performance has been greatly ignored. The study in this chapter is the initial step into the examination of how oscillatory activity during physical exercise is modulated and how this correlates to long-term memory performance. It is important to iterate that whilst a few studies have recorded EEG during an ongoing exercise task (Ciria et al., 2018), EEG data in this study was recorded during the brief 1 min rest every 4 min of exercise on the cycle ergometer. This was done to minimise the signal to noise ratio as a result of movement during the exercise task and to minimise the number of removed components of spatial confounds, with the fundamental aim of obtaining cleaner and more reliable recordings. Some could argue that this may be resting state EEG, however, as the interval was measured within a few seconds after cycling, participants were unlikely to have returned to resting state in that time frame. For example, Spring and colleagues found that after a 25 min bout of cycling, recovery of the autonomic cardiovascular system remained uncompleted even after 1 hr of exercise cessation. Furthermore, MacDonald and colleagues showed that the effects of exercise on blood pressure are observed up to 45 min post-exercise (MacDonald et al., 2000). Additionally, Crush and colleagues also found that the positive exercise-induced effects on mood remained even after a 30 min recovery period (Crush et al., 2018).

The results provided in this chapter do not originate from a new study. Instead, they are a part of Study 2 (see Chapter 2, section 4.2). In Study 2, EEG was used during the physical exercise sessions. This chapter aims to investigate the correlations between neural oscillatory activity during physical exercise and enhanced long-term memory performance.

2. Introduction

For almost a century, researchers have been using EEG to record electrical activity in the human brain. EEG can invasively (intracranial EEG) and non-invasively (scalp EEG) record neural signals comparable to the local field potential in the cortex but on a significantly larger spatial scale (Sauseng & Klimesch, 2008). EEG recordings can provide insight into the neural activity from the entire cortex thereby allowing researchers to study the interactions between different brain areas and different cortical networks (Sauseng & Klimesch, 2008).

One of the main drawbacks of EEG is its low spatial resolution (a few centimetres). However, EEG recordings provide excellent temporal resolution (a few milliseconds) allowing for real-time neural recordings. This, in particular allows for the analysis of oscillatory activity in the brain, which is the focal point of this chapter. Brain oscillations are considered a core neural mechanism for storage and retrieval of long-term memories and refer to the synchronous fluctuations in the local field potential between excitation and inhibition, which induce synchronised firing patterns (Hanslmayer et al., 2012).

Over the past few decades, the strong links between synchrony and synaptic plasticity have sparked growing interest in the role of brain oscillations for memory formation (Hanslmayer & Staudigl, 2014). Earlier research was limited to simple parameters and specific frequency bands due to the limited computational power available at the time. However, today, research has expanded to several frequency bands and more complex analysis (Hanslmayer & Staudigl, 2014). This larger array of data demonstrates the complexity of the relationship between brain oscillations and memory.

Based on functional differences, neural oscillations are classified into different bands. The main bands include alpha, beta, theta, gamma, and delta. Alpha wave oscillations typically occur at a frequency range of 7-13 Hz (Khader et al., 2010) and are considered an idling rhythm of the occipital cortex as they primarily originate from the occipital lobe, specifically during eyes-closed wakeful rest (Kropotov, 2009). Beta wave oscillations have a frequency range of 13-30 Hz, have been extensively studied in states of normal waking consciousness, and linked to attention and cognition (Rangaswamy et al., 2002). Gamma wave oscillations occur at frequencies from 30 Hz and above (Jensen & Mazaheri, 2010) and are linked to cognitive functions such as attention and working memory (Benchenane et al., 2011). Delta wave oscillations (0.1-3 Hz) hint at functional correlates in cognitive processing (Başar et al., 1999). Lastly, theta wave oscillations, which occur at a frequency range of 4-7 Hz (Sauseng et al., 2006), are strongly linked with an important role in memory formation (Osipova et al., 2006).

Traditionally, theta wave oscillations were the targeted focus in memory studies as they are typically associated with facilitating synaptic plasticity and have been shown to affect memory via depolarisation (Asada et al., 1999; Buzsáki, 2005; Pape et al., 2005; Rutishauser et al., 2010). This depolarisation induces the opening of NMDA channels, which results in synaptic modification and memory formation via the subsequent cascade of molecular processes (for review: Nyhus & Curran, 2010).

In a review by Klimesch (1999) it was noted that enhancements in memory performance may be attributed to two type of EEG phenomena: tonic decreases and phases increases in theta power (Klimesch, 1999). Phasic changes in theta power suggest that theta synchronisation is positively correlated with successful encoding of new information, which is reflected by theta oscillatory activity in the cortico-hippocampal feedback loops (Klimesch, 1999). Klimesch also highlighted that alpha wave activity responds in the opposite direction to theta, where increased task demands lead to increased theta power (synchronisation) and decreased alpha power (desynchronisation) (Klimesch, 1999).

Further, the dorsolateral prefrontal cortex has been suggested to aid the ordering of new information for episodic encoding and retrieval, maintain temporal context, and retrieve associated memory representations when a particular cue is presented during retrieval (Nyhus & Curran, 2010). Several studies have shown consensus for the notion that theta phase synchronisation between frontal and posterior regions of the brain modulates retrieval of episodic memories (for review: Nyhus & Curran, 2010). Additionally, some studies have reported early increases in theta power over frontal scalp locations, which further supports the role for theta phase synchronisation in modulating retrieval of episodic memories. Late increases in theta power over frontal scalp locations have also been reported, indicating a role for theta oscillations in post-retrieval processing (for review: Nyhus & Curran, 2010).

On a different note, findings from intracranial EEG (iEEG) studies contradict the majority of findings from scalp EEG studies as well as the theta hypothesis which directly implicates the theta rhythm, specifically increases in theta power, in the successful formation of declarative memory (for review: Herweg et al., 2020). It was suggested that this discrepancy can only be fully answered with simultaneous recordings of scalp and iEEG in the same subjects, but was hypothesised that this discrepancy may be a result from differing scales of spatial resolution between the two recording techniques (Herweg et al., 2020).

Hanslmayr and colleagues (2012) found that studies demonstrating a crucial role for brain oscillations in long-term memory typically ascribe that towards increased theta and gamma synchronisations (Hanslmayr et al., 2012). Gamma wave oscillations are strongly linked to role in attention, and the encoding and recall of long-term memories (Jensen et al., 2007). Sustained neuronal firing in the gamma frequency band has also been implicated in the active maintenance of working memory representations (Jensen et al., 2007).

Gamma wave synchronisation is associated with successful encoding of long-term memories. This has been demonstrated via neural synchronisation of memory representations in the areas of the brain that receive and process sensory information, which results in stronger neural firing, and consequently stimulates synaptic plasticity (Jensen et al., 2007). Furthermore, gamma wave synchronisation is also associated with successful retrieval of long-term memories as demonstrated by increased activity in the gamma frequency in occipital areas during successfully recalled items compared to the rejection of new items (Jensen et al., 2007; Osipova et al., 2006).

Nyhus and Curran (2010) highlight other functional roles of gamma and theta oscillations in episodic memory: (a) both gamma and theta oscillations allow for transient interactions between cortical structures and the hippocampus for encoding and retrieval, (b) gamma wave synchronisation binds perceptual and contextual information from several brain areas into episodic representations, and (c) these episodic representations are temporally ordered by theta wave oscillations (Nyhus & Curran, 2010).

While theta and gamma oscillations are most commonly investigated for their roles in long-term memory, recent studies have shown that alpha and beta oscillations may also play an equal role (Fell et al., 2011; Hanslmayer et al., 2012; Hanslmayer & Staudigl, 2014). New data suggests that decreases in alpha and beta oscillatory activity are also linked to encoding and retrieval of long-term memories (Burke et al., 2013; Guderian et al., 2009; Hanslmayr et al., 2012; Hanslmayr & Staudigl, 2014).

Klimesch and colleagues (1996) were one of the first researchers to demonstrate a link between decreased alpha power during encoding and enhanced retrieval (Hanslmayr et al., 2012; Klimesch, Doppelmayr, Pachinger, & Ripper, 1997; Klimesch, 1996, 1999). Klimesch and colleagues found that alpha oscillations engage the thalamo-cortical network and a significant increase in alpha desynchronisation was found during semantic judgement tasks (Klimesch, Doppelmayr, Schimke, & Ripper, 1997; Klimesch, 1999; Klimesch et al., 2008; Nyhus & Curran, 2010). Importantly, these alpha power decreases were observed during responses to an old/new recognition task where the stimuli were visually presented words (Düzel et al., 2003; Hanslmayer et al., 2012). In another study, strong alpha power decreases were observed over the left parietal region for word-based stimuli and over the right parietal region for face-based stimuli (Burgess & Gruzelier, 2000; Hanslmayer et al., 2012).

These alpha power decreases were in conjunction with lower beta power decreases during successful recognition of words and faces in the aforementioned recognition task (Burgess & Gruzelier, 2000). More recent studies also found decreased beta power for subsequently remembered items in the hippocampus and the left and right lateral temporal lobes (Hanslmayer et al., 2009; Sederberg et al., 2007). However, Hanslmayr and colleagues found that these decreases in beta power were exclusive to semantic encoding (Hanslmayer et al., 2009, 2012). Together these power decreases in alpha and beta waves may indicate the reactivation of the sensory features of a memory trace (Hanslmayer et al., 2012).

Conversely, a few studies reported alpha band power increases for subsequently remembered stimuli (Khader et al., 2010). However, unlike the aforementioned studies that recorded alpha band desynchronisation during item presentation (Klimesch, Doppelmayr, Schimke, et al., 1997), this increased alpha band power was observed during a presentation-free period where participants were instructed to rehearse the stimuli (Hanslmayer et al., 2012; Khader et al., 2010). Recent studies put forward the idea that alpha power is able to regulate the flow of information in the cortex via the inhibition of task irrelevant regions (Hanslmayr et al., 2012; Jensen & Mazaheri, 2010; Klimesch, Sauseng, & Hanslmayr, 2007). As such, Hanslmayr and colleagues postulated that the observed alpha band power increase in these studies could be interpreted as the deactivation of task irrelevant visual processing areas during the maintenance of items in working memory (Hanslmayer et al., 2012). Similarly, Hanslmayr and colleagues (2012) also posit that the alpha band power decreases in the cortex observed during item presentation may reflect the activation of encoding-relevant brain regions (Hanslmayer et al., 2012).

Interestingly, theta activity was not affected by the semantic task demands described above and Klimesch proposed that theta band synchronisation (increased theta power) reflects episodic memory and the encoding of new information (Klimesch, Doppelmayr, Schimke, et al., 1997; Klimesch, 1999). This was demonstrated by a significant increase in theta synchronisation and power for successfully remembered words (Klimesch, Doppelmayr, Schimke, et al., 1997; Klimesch, 1999; Nyhus & Curran, 2010). These findings are consistent with other studies that link alpha and beta rhythm to semantic memory (for consistently phase desynchronising for semantically related items), and theta rhythm to episodic memory (for consistently phase synchronising for episodically related items) (for review: Nyhus & Curran, 2010).

Lastly, whilst only a few studies have investigated delta band oscillations during cognitive processing (Harmony, 2013), delta oscillations appear to be implicated in motivational processes. In his review, Knyazev (2012) suggests that this fits into the hypothesis that delta oscillations represent the most basic evolutionary old oscillatory mode, which dominated in lower vertebrates, but also is still associated with primary human processes (Knyazev, 2012). Knyazev stated that in waking adults, delta oscillations are overshadowed by higher frequency oscillations that are strongly linked to more advanced and operationally flexible processes (Knyazev, 2012). Delta oscillations seem to increase when more advanced systems lose priority. For example, increased delta oscillations are observed during early developmental stages, as well as during sleep, and importantly for clinical EEG researchers, are linked to certain pathological states (Knyazev, 2012). Functionally, synchronisation of delta oscillations have been shown to occur during semantic tasks in children (Harmony, 2013), and have been linked to behavioural inhibition (Knyazev, 2012). Further, a recent study found that delta wave oscillations modulate the efficacy of processes involved in promoting memory consolidation during sleep by promoting the weakening of memories (Kim et al., 2019). In other words, delta wave oscillations mediate the weakening of memory reactivations and promote forgetting (Kim et al., 2019).

These studies have shown that episodic and semantic memories are affected by different neural rhythms. However, it is important to iterate that, while episodic and semantic memories are distinct, in actuality it is challenging to separate the associated rhythms due to the commonality between the two memory types. Semantic memories (facts, concepts) may be originally encoded via episodic processes, and episodic memories (events, experiences) may depend on semantic elaboration (Nyhus & Curran, 2010). Furthermore, there is no comprehensive mapping of oscillatory rhythms to specific cognitive processes. That is, while oscillations from multiple frequencies can affect a single cognitive process, oscillations of a single frequency in one brain region, functioning on a cognitive process, can affect a different cognitive process in another brain region (Başar et al., 1999; Kahana, 2006; Klimesch et al., 2008; Nyhus & Curran, 2010).

These complex interactions result in a common problem for researchers in determining how functionally specialised brain areas interact to perform rich cognitive tasks. Whilst neurons that are physically close to one another (local assemblies) process information, the neurons that are spread across different brain regions (global assemblies) combine several processes necessary for higher-level cognitive processing (Nyhus & Curran, 2010). The processing and transfer of information in the local assemblies happens during faster, higher frequencies, whereas communication in global neural assemblies tends to occur during slow, lower frequencies (Nyhus & Curran, 2010). However, there is evidence for oscillatory multiplexing, whereby oscillations of different frequency bands share a common neural substrate (Fries, 2005; Gu et al., 2015; Nyhus & Curran, 2010). This further highlights some of the difficulties in the study of oscillatory activity and information processing as this multiplexing allows for the reconfiguration of effective connectivity such that faster oscillations communicate content whilst slower oscillations mediate transient connectivity (Akam & Kullmann, 2010; Fries, 2005; Gu et al., 2015; Nyhus & Curran, 2010).

The aim of this chapter is to investigate the correlation between neural oscillatory activity during physical exercise and enhanced long-term memory. This will be done by (a) using EEG during physical exercise to record neural activity, and (b) using the old/new recognition task to detect physical-exercise-induced enhancements to long-term memory performance. Where there are enhancements in long-term memory performance, the EEG data will help determine which neural oscillatory frequency or frequencies is/are correlated to enhancements in long-term memory performance.

3. Hypotheses

H1: Theta band oscillations will be positively correlated with memory performance. The majority of theta band oscillations will be detected in frontal electrodes.

H2: Alpha band oscillations will be negatively correlated with memory performance. Alpha band oscillations are expected to appear around central electrodes.

H3: Beta band oscillations will be negatively correlated with memory performance. Beta band oscillations are expected to appear in frontal electrodes.

H4: Gamma band oscillations will be positively correlated with memory performance. Gamma band oscillations are expected to appear in central and/or temporal electrodes.

4. Methods

4.1 EEG Recording

EEG was recorded during the brief 1 min rest in each exercise block on the cycle ergometer. This was done to minimise the signal to noise ratio as a result of movement during the exercise task and to minimise the number of removed components of spatial confounds, with the fundamental aim of obtaining cleaner and more reliable recordings.

EEG was recorded continuously from 64 Ag/AgCl electrodes with a BrainVision QuickAmp-72 amplifier system (Brain Products, Germany) placed according to the 10 – 20 electrode placement system (including electrodes; Fp1, Fp2, AF7, AF3, AF4, AF8, F7, F5, F3, F1, Fz, F2, F4, F6, F8, FT7, FC5, FC3, FC1, FC2, FC4, FC6, FT8, T7, C5, C3, C1, Cz, C2, C4, C6, T8, TP9, TP7, CP5, CP3, CP1, CPz, CP2, CP4, CP6, TP8, TP10, P7, P5, P3, P1, Pz, P2, P4, P6, P8, PO9, PO7, PO3, POz, PO4, PO8, PO10, O1, Oz, O2, and ground and reference electrodes). Fp1 and Fp2 electrodes were placed directly below and near the outer corner of the right eye to record vertical and horizontal eye movements. Fp1 and Fp2 electrodes were chosen as the electrooculography (EOG) electrodes due to the limitation of the EEG system available as it did not have any EOG input. Raw EEG was sampled at 512 Hz with 12- bit resolution. Markers were placed at the beginning of each rest period and at the beginning of the cycling exercise. For analysis, the first 4s from the first marker at the beginning of the rest period were ignored to allow participants to get into a resting position, after which epoching took place.

4.2 Analysis of EEG Data

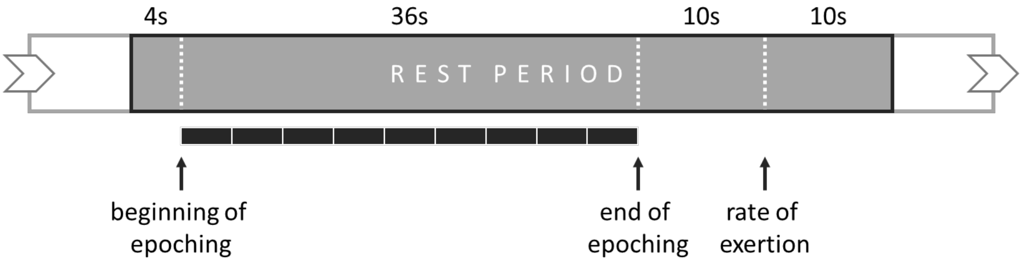
Here, the interest was to infer the neural correlate of brain oscillatory activity during physical exercise with memory performance. EEG data were analysed using SPM v12 (statistical parametric mapping, Wellcome Trust, London, UK). Three faulty electrodes were excluded from all analysis (FC6, TP7, TP10) due to persistent high noise across all participants. Due to the atypical and active setting for EEG, I took note of indicators that will allude to the quality of the data. For instance, the average number of faulty electrodes and average number of excluded epochs (further below). The average number of faulty electrodes: (mean[SD]): 6.73 [2.31], which is 10.51[3.60]%, with a median score of 7. Data was filtered for 0.5 – 54 Hz using 7th order Butterworth filter, baselined based on average electrode activity, and down sampled to 128 Hz data. Then, eye-blinks were removed using activity of the Fp2 electrode and the topography-based artefact correction method: spatial confounds were indicated based on Singular Value Decomposition (SVD) mode and sensor data was corrected using Signal-Space Projection (SSP) correction mode. A maximum of two components of spatial confounds were removed from the EEG data. If the removal of more than two components was needed, participants were subsequently excluded (n = 4). Subsequently, data was epoched based on the onset of the Rest periods. The first 4s and the last 20s of the 1 min Rest period were ignored. This was done to avoid contaminating the data with the brain activity due to the slow-down following the onset of the Rest period, and response to the rate of exertion question (Borg Rating of Perceived Exertion) at 10s prior to the end of the Rest period, Figure 16. Nine 4s epochs were then extracted for data analysis for each block of rest in between exercise. The average number of excluded epochs (mean[SD]): 12.26 [8.79], which is 20.43[14.65]%, with a median score of 11.

Time-frequency analysis was then conducted using Morlet wavelet transform across 1 – 50 Hz with wavelet cycle of 7 and subsample of 1. Subsequently, data in all epochs were Log-ratio baseline corrected to the nine epochs during the Rest period following the Warm-up period. Then, the time-frequency data was averaged across time in each epoch. Finally, the average of all the epochs were calculated for each participant for subsequent data analysis.

The final data consisted of frequency activity averaged over time for each electrode for each participant. Correlation of frequency activity and memory performance is then calculated for of each frequency and each electrode. Based on the p values, FDR corrected p value for multiple comparison is calculated (Benjamini & Hochberg, 1995; Benjamini & Yekutieli, 2001).

Figure 16.

Procedure of epochs during the rest period.



Note: The first 4s and last 20s of the Rest period were ignored. Subsequently, 9 epochs of 4s were extracted.

5. Results

A Pearson's correlation was run to determine the relationship between a participant's memory performance and oscillatory activity in the brain. Figure 23 shows correlations (both p and r values) between oscillatory activity and memory performance during physical exercise at all recorded frequencies. Significant correlations between a frequency band and enhanced memory performance are shaded. Figures 1 – 5 are visual representations of the electrodes that recorded significant correlation between delta (Figure 17), theta (Figure 18), alpha (Figure 19), beta (Figure 20), and gamma (Figure 21) band oscillations and enhanced memory performance during moderate-intensity physical exercise. Figure 22 overlays all the different frequencies into one visual representation.

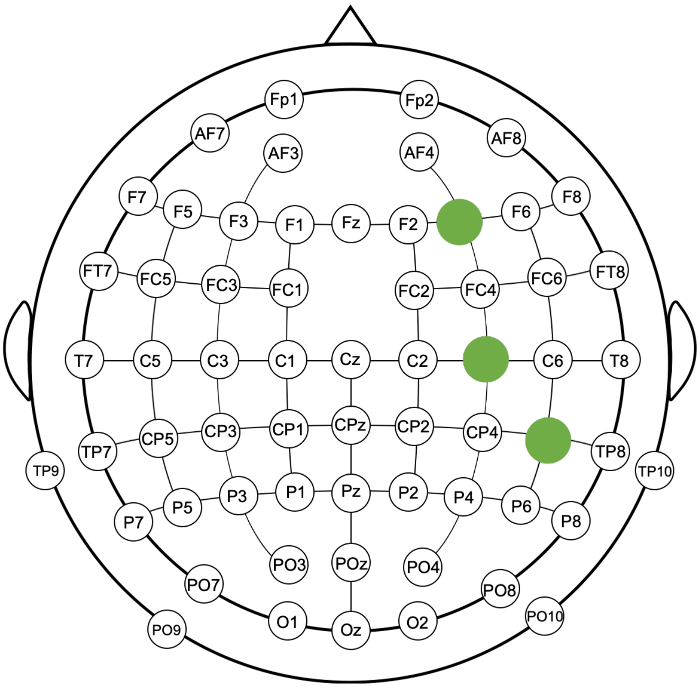
5.1 Delta band oscillations

Significant delta band oscillations were detected in one frontal, one central and one centroparietal electrode (F4, C4, CP6; see Figure 23, P value). These are also represented in Figure 17 to visually identify electrode location to brain area.

A Pearson's correlation was run to determine the relationship between a participant's memory performance and delta band oscillatory activity. Delta oscillations in the prefrontal, frontal, and central areas of the brain had a positive correlation with memory performance (Figure 23, R value).

Figure 17.

Visual representation of electrodes recording significant correlation between delta wave oscillations and enhanced memory performance during moderate-intensity physical exercise.



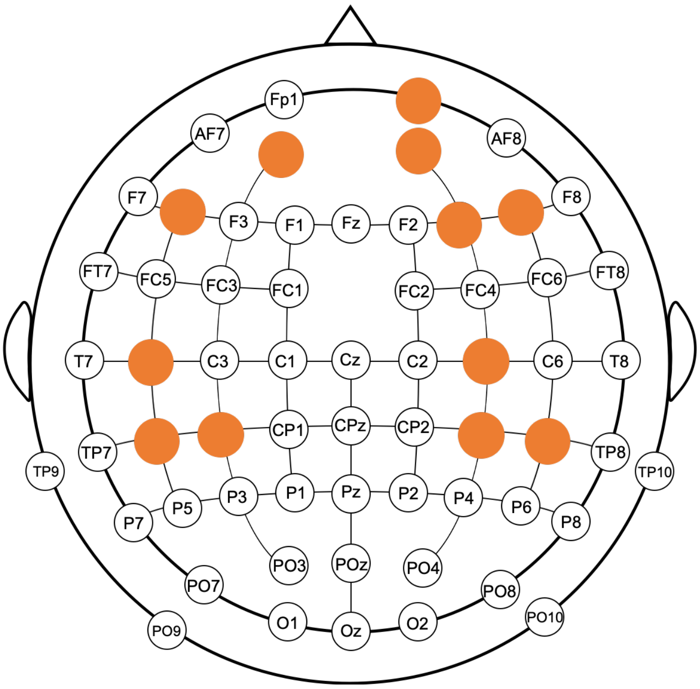
5.2 Theta band oscillations

The prefrontal and frontal electrodes, representative of the frontal lobe, were predominated by theta band oscillations (Fp2, AF3, AF4, F5, F4, F6; see Figure 23, P value). Significant theta band oscillations were also detected in central electrodes (C5, C4, CP5, CP3, CP4, CP6; see Figure 23, P value). These are also represented in Figure 18 to visually identify electrode location to brain area.

A Pearson's correlation was run to determine the relationship between a participant's memory performance and theta band oscillatory activity. Theta oscillations in the prefrontal, frontal, and central areas of the brain had a positive correlation with memory performance (Figure 23, R value).

Figure 18.

Visual representation of electrodes recording significant correlation between theta wave oscillations and enhanced memory performance during moderate-intensity physical exercise.



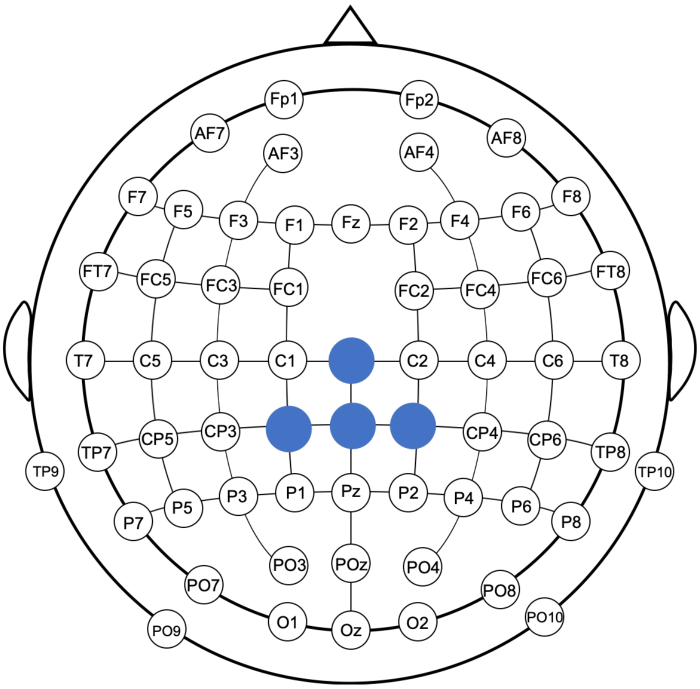
5.3 Alpha band oscillations

The centremost central electrodes were solely predominated by alpha band oscillations (Cz, CP1, CPz, CP2; see Figure 23, P value). This is represented in Figure 19 to visually identify electrode location to brain area.

A Pearson's correlation was run to determine the relationship between a participant's memory performance and alpha band oscillatory activity. Alpha oscillations in the central areas of the brain had a strong, negative correlation with memory performance (Figure 23, R value).

Figure 19.

Visual representation of electrodes recording significant correlation between alpha wave oscillations and enhanced memory performance during moderate-intensity physical exercise.



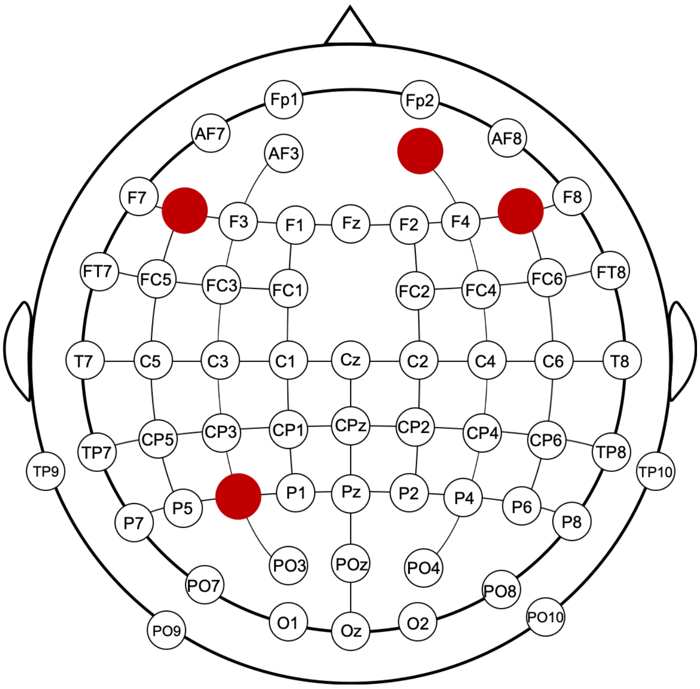
5.4 Beta band oscillations

Significant beta band oscillations were detected in one prefrontal electrode, some frontal and central-parietal electrodes, and one temporoparietal electrode, all generally in the periphery (AF4, F5, F6, P3; see Figure 23, P value). This is represented in Figure 20 to visually identify electrode location to brain area.

A Pearson's correlation was run to determine the relationship between a participant's memory performance and beta band oscillatory activity. Beta oscillations in the frontal, and central-parietal areas of the brain had a positive correlation with memory performance, except for oscillations in the P3 electrode, which were negatively correlated with memory performance (Figure 23, R value).

Figure 20.

Visual representation of electrodes recording significant correlation between beta wave oscillations and enhanced memory performance during moderate-intensity physical exercise.



5.5 Gamma band oscillations

Significant gamma band oscillations were detected in one frontal, two centroparietal electrodes, as well as one parietal electrode (F6, CP5, CP6, P3; see Figure 23, P value). This is represented in Figure 21 to visually identify electrode location to brain area.

A Pearson's correlation was run to determine the relationship between a participant's memory performance and gamma band oscillatory activity. Gamma oscillations in the frontal, and central-parietal areas of the brain had a positive correlation with memory performance (Figure 23, R value).

Figure 21.

Visual representation of electrodes recording significant correlation between gamma wave oscillations and enhanced memory performance during moderate-intensity physical exercise.

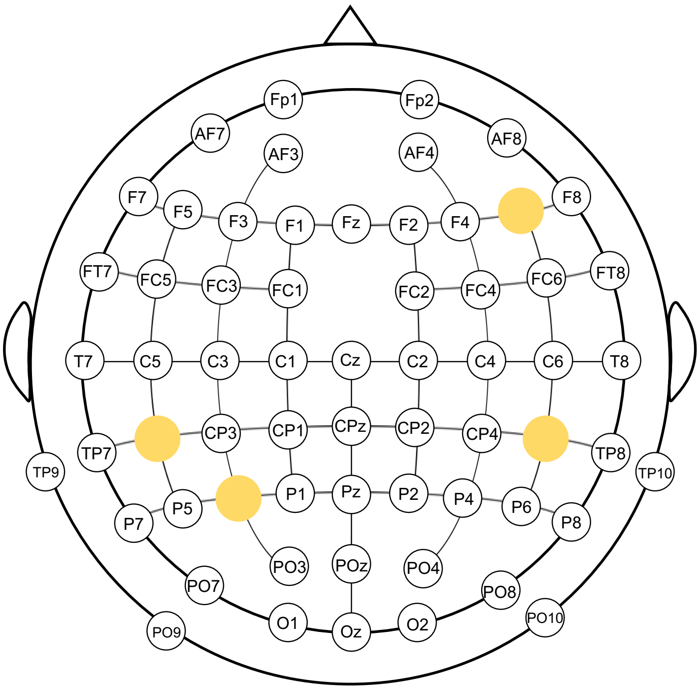
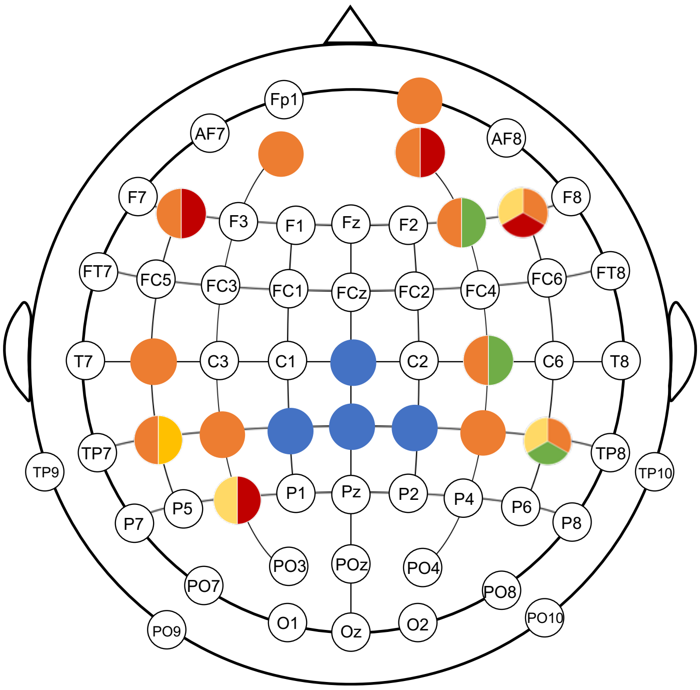


Figure 22.

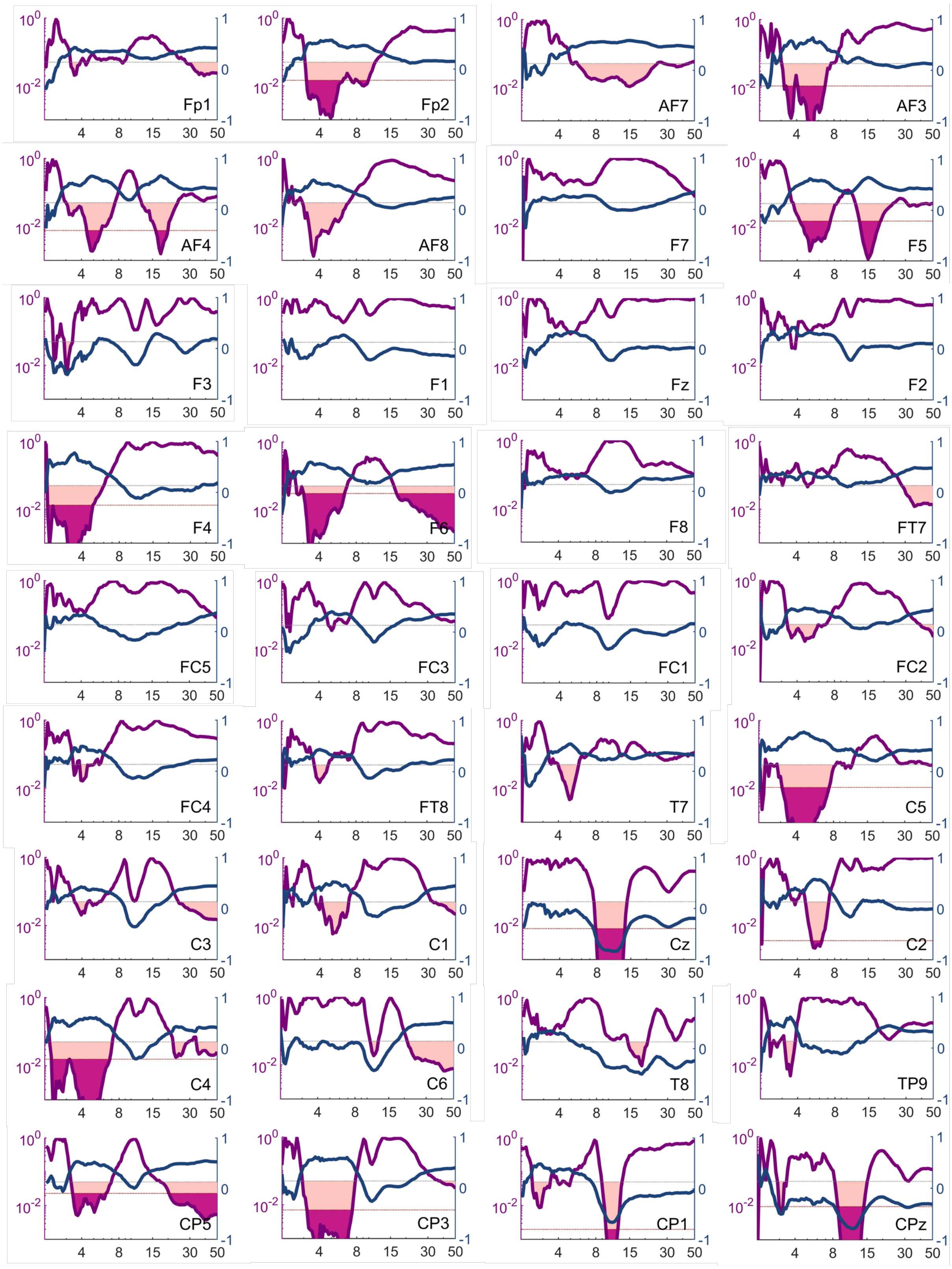
Visual representation of electrodes recording significant correlation between oscillations and enhanced memory performance during moderate-intensity physical exercise.

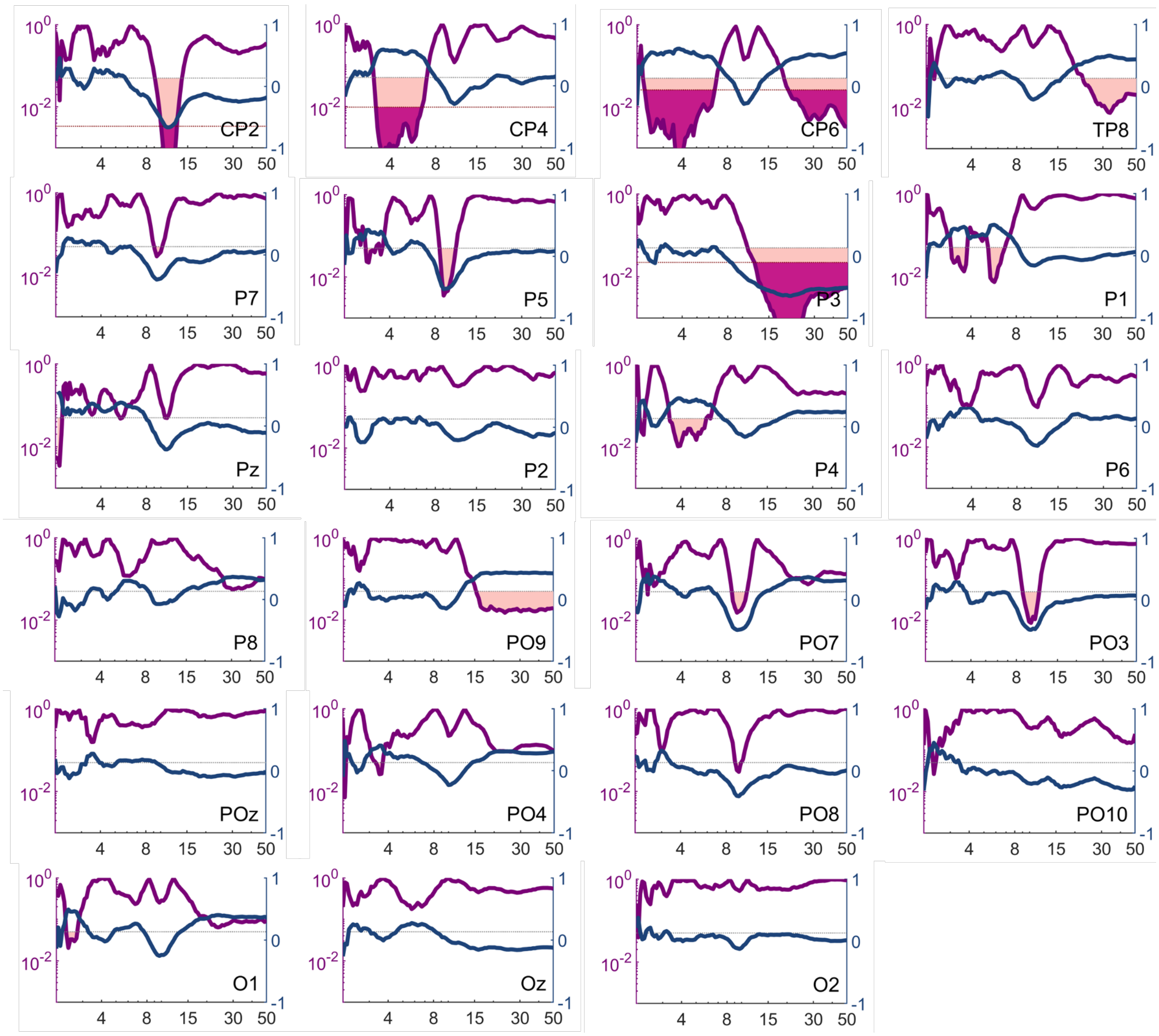


Note: Theta: orange; alpha: blue; delta: green; beta: red; gamma: yellow.

Figure 23.

P and R values of significant oscillatory activity during physical exercise.





Note: The purple line and the left axis indicate p value. The blue line and the right axis indicate r values. Significant *p* value correlations between frequency power and memory performance during moderate-intensity physical exercise intervention are shaded in a lighter shade ($p < 0.05$) and darker shade (FDR corrected for multiple comparisons p threshold). R value is indicative of the direction of correlation (positive or negative) between oscillatory activity and memory performance. The horizontal and vertical axes are logarithmic to have a clearer view of the lower frequencies and p values. Frequency bands: Delta (< 4 Hz), Theta (4-8 Hz), Alpha (8-15 Hz), Beta (15-30 Hz), Gamma (>30 Hz).

6. Summary

The aim of this chapter was to investigate the correlation between neural oscillatory activity during physical exercise and enhanced long-term memory performance. This was achieved by recording EEG during the physical exercise sessions of study 2 (see Chapter 2, section 4.2)

Results obtained from EEG data indicate significant positive correlations for delta, theta, beta, and gamma band oscillations, and a significant negative correlation for alpha band oscillations with memory performance.

Theta band oscillations were primarily present in prefrontal and frontal electrodes, as well as in central/parietal electrodes. This is in line with the literature, which indicates a positive correlation and phase synchronisation in frontal regions of the brain (Klimesch, 1999; Nyhus & Curran, 2010) as well as right parietotemporal areas (Osipova et al., 2006).

Significant alpha band oscillations were only detected in four electrodes, all of which were centrally located and clustered together. Alpha band oscillations were negatively correlated with memory performance and this is supported by the literature, which suggests that alpha activity responds in the opposite direction to theta (Klimesch, 1999) and engages the thalamocortical network (located centrally, and would appear on the same electrodes that detected alpha activity) (Klimesch, 1999; Klimesch et al., 2008; Klimesch et al., 1997).

Beta band oscillations were primarily positively correlated to memory performance except for the oscillations detected on one parietal electrode. Generally, the literature points towards a negative correlation between beta activity and memory performance (Guderian et al., 2009; Hanslmayr et al., 2012). Additionally, the literature suggests decreases in beta power for subsequently remembered items in the lateral regions of the left and right temporal lobes (Hanslmayer et al., 2009; Sederberg et al., 2007). Whilst the standard EEG 10-20 system only provides limited coverage of the temporal regions (Mani, 2014), significant beta activity was detected around the electrodes clustered over the left and right temporal lobes (Montoya Martinez et al., 2019).

Significant gamma band oscillations were primarily detected in centroparietal electrodes with a couple in lateral frontal electrodes. These gamma oscillations were positively correlated with memory performance. Whilst the literature also indicates a positive correlation for gamma activity and memory performance (Jensen et al., 2007; Osipova et al., 2006), the literature, however, suggests significant gamma activity originating from the occipital lobe, particularly Brodmann areas 18 and 19 for enhanced declarative memory performance (Osipova et al., 2006).

6.1 Considerations

Memory performance was tested using an old/new recognition task. On average, memory performance scores across all three interventions (moderate-intensity physical exercise, active wakeful rest, passive wakeful rest) were relatively high (over 75%; see Chapter 2, Study 2). It would be of interest to investigate the effects of these interventions using a free recall task. Recognition, as opposed to free recall, does not require depth of processing, which is the amount of cognitive effort required to obtain information (Lockhart et al., 1976). By employing a free recall task, cognitive demand to recall an item would significantly increase due to the lack of retrieval cues, and consequently, make the recall task more difficult. Consequently, the cognitively more challenging free recall task may lead to greater differences in memory performance scores between the interventions. Additionally, Staresina and Davachi (2006) investigated encoding mechanisms that support free recall and their relationship to those that support other forms of recognition memory. They found evidence for encoding mechanisms specific to free recall that did not support later associative recognition compared with item recognition (Staresina & Davachi, 2006). Interestingly, these effects, specific to free recall, were observed in the left DLPFC, which is the area of tDCS stimulation for the studies in Chapter 3.

The data from this chapter provide insight into the behaviour of neural oscillations during physical exercise in University students (M_{age} = 19.8) when enhanced memory performance is observed. It would be interesting to investigate whether these neural oscillations differ in older adults and/or in a patient population (e.g. forms of dementia such as mild cognitive impairment or Alzheimer's disease). The results from such a study could have major implications in the treatment of patients with memory deficiencies and could highlight the importance of physical exercise in the older population, and particularly in care homes with patients suffering from dementia.

6.2 Conclusion

The data from this study indicate significant positive correlations for delta, theta, beta, and gamma band oscillations, and a significant negative correlation for alpha band oscillations with memory performance. The majority of these results fall in line with the literature, and the interactions between different frequencies (e.g. theta-alpha interaction; Klimesch, 1999) occurred as expected. However, beta oscillations in this study were found to have a positive correlation with memory performance, whilst many studies indicate a negative correlation. However, some studies have shown an increase in beta power after acute physical exercise (Moraes et al., 2007), and this increase has been linked to enhanced cortical activation, and therefore, to attention and memory as well. Further study will be required to determine the nature of beta oscillations in physical-exercise-induced memory enhancement.

Chapter 5: General discussion

This thesis investigated the modulatory effects of physical exercise, wakeful rest, and transcranial electrical brain stimulation on long-term memory and their associated neural oscillatory activity. The investigations were categorised into three chapters. (a) Chapter 2 investigated the effects of physical exercise and wakeful rest. (b) Chapter 3 compared the effects of moderate-intensity continuous, acute physical exercise to transcranial direct current stimulation, and whether a combination of these two interventions would elicit further memory modulation. (c) Chapter 4 examined how oscillatory activity during physical exercise is correlated to long-term memory performance. As such, this chapter will follow the same approach by discussing the findings of this thesis in three distinct sections.

1. The effects of physical exercise and wakeful rest on long-term memory

The aim of Chapter 2 was to determine the most effective post-encoding protocol of physical exercise on long-term memory enhancement, whilst also comparing it to two forms of wakeful rest (active and passive). To investigate these aims, three studies were run where performance accuracy on an old/new recognition task was assessed. The first study examined the effects of different intensities of continuous, acute physical exercise. The second study compared continuous, acute physical exercise to passive rest and active rest, and the third study compared continuous, acute physical exercise to high-intensity interval training (HIIT) and passive rest.

The main finding across the three studies was that continuous, acute physical exercise performed at a moderate intensity was optimal for enhancing long-term memory performance. These studies also demonstrated that short periods of uninterrupted wakeful rest (passive rest) after learning can increase the likelihood of remembering at a later time.

1.1 Physical exercise intensity

A study by Hötting and colleagues (2016) assessed the effects of single bouts of low (<57% HR_{max}) and high intensity (~80% HR_{max}) physical exercise on memory consolidation and found no significant enhancements at either intensity. Instead, results showed that participants in the rest group (control) recalled more words than either exercise group (Hötting et al., 2016). In Study 1 (Chapter 2), results indicate superior memory recall at moderate intensity physical exercise compared to high-intensity ($p = 0.002$), and approaching significance compared to low-intensity ($p = 0.037$, however, statistical confidence has been adjusted to $p < 0.011$ to correct for multiple comparisons using FDR). Together, this suggests an inverted-U relationship between physical exercise intensity and memory performance. Whilst not explicitly obvious at first, this falls in line with the notion that increased intensity leads to increased arousal (Brisswalter et al., 2002). Easterbrook's cue utilisation theory (1959) better clarifies this intensity-arousal relationship, which predicts that optimal performance corresponds to an intermediate level of arousal. By way of illustration, as arousal increases, focus is tapered and consequently directs the processing of relevant cues and the filtering out of irrelevant cues. However, if arousal becomes too high, relevant cues will also be filtered out and result in the reduction of the availability of important cues. Specifically, over-arousal results in the filtering out of relevant cues, and under-arousal allows for a significant influx of irrelevant cues (Brisswalter et al., 2002; Easterbrook, 1959; Kent, 2006).

Nevertheless, the effect of physical exercise intensity on memory is likely influenced by several factors that should not be overlooked. All of the studies in this thesis used images as stimuli and an old/new recognition task to specifically engage the declarative memory domain of long-term memory. Given the complex relationship between physical exercise and memory, employing different cognitive tasks, or engaging different memory domains may yield different outcomes. For example, Thomas and colleagues (2016) administered 15 min of high-intensity physical exercise after learning a visuomotor accuracy tracking task. This task engages a subset of the non-declarative memory domain; procedural memory. When testing procedural memory, high intensity physical exercise produced significant enhancements in motor skill retention compared to low intensity physical exercise and control groups (Thomas et al., 2016). Similar to Hötting and colleagues (2016), Thomas and colleagues (2016) also proposed that physical exercise intensity can modulate memory consolidation. However, in reference to motor skill learning, Thomas and colleagues suggested a dose-response relationship in favour of higher intensities of physical exercise to augment offline effects and strengthen procedural memory; the higher the intensity the more pronounced the consolidation of long-term procedural memory (Thomas et al., 2016).

Another factor influencing the effect of physical exercise intensity on long-term memory includes the onset of physical exercise relative to cognitive task. For example, Chang and colleagues (2012) revealed that physical exercise intensity did not moderate the effects on memory when the cognitive task was administered during physical exercise (Chang et al., 2012). However, when the cognitive task was administered immediately following exercise, physical exercise intensity had a significant positive effect at low to moderate intensities. Further, Chang and colleagues also reported that when the cognitive task was administered after a delay following exercise, memory performance was negatively affected by low intensities, but positively affected by moderate to high intensities (Chang et al., 2012).

The duration of the physical exercise intervention has also been shown to modulate the effect of physical exercise intensity on long-term memory performance. That being said, there is a notable lack of empirical studies aimed at testing the effects of physical exercise duration on memory. In another study by Chang and colleagues (2015), 20 min of moderate intensity physical exercise led to significantly better recall than 10 min or 45 min of the same physical exercise intervention (Chang et al., 2015).

In sum, the literature supports the results from Study 1 in that physical exercise interventions performed after encoding optimally enhance long-term memory when performed at a moderate intensity.

1.2 Wakeful rest

A study by Dewar and colleagues (2012) investigated the effects of passive and active rest on long-term memory. The authors presented participants with a story-learning phase (encoding) followed by a period of passive wakeful rest or spot-the-difference game (active rest). Dewar and colleagues found that even a brief 10 min period of passive wakeful rest after encoding allowed for the new memory traces to be better consolidated and retained for longer (significant enhancements still noticeable 7 days post-encoding) (Dewar et al., 2012). Although the results from Study 2 (Chapter 2) showed a higher performance accuracy score for passive rest (78%) compared to active rest (75%), no significant difference between the two was found ($p = 0.336$). Whilst this is mostly in contrast to the literature (for review: Wamsley, 2019), several factors could account for this. First, a shorter wakeful rest period should be considered. Study 2 employed a 30 min period of wakeful rest. Typically, the longer the rest period the more likely the reduced mobility and reduced number of external stimuli present during passive rest will augment a heightened relaxed mental state and possibly hypnagogic. Consequently, this would induce fogginess, decrease alertness, and increase sleep propensity. All participants in Study 2 completed a Stanford Sleepiness Scale and reported a level between 1-3. However, whilst participants were encouraged to report truthfully, some may have felt reluctant to report a higher number to avoid being excluded from the study or upsetting the experimenter. On that basis, and on the basis that other studies have reported passive-rest-induced memory enhancements for periods as short as 10 min (Dewar et al., 2012), reducing the 30-min period of wakeful rest employed in this study may alleviate the sleepiness and drop in alertness typically seen with longer periods of wakeful rest.

Memory studies using a passive wakeful rest condition typically use one of two states: an eyes-open or eyes-closed state. The literature demonstrates that this differentiation has a considerable influence on the effects of passive rest on memory (Brokaw et al., 2016; Dewar et al., 2012; Kuschpel et al., 2015c; Marx et al., 2004). An eyes-open passive rest condition was employed in Study 2 to (a) monitor and have visual confirmation of any participants that may be entering a hypnagogic state during the 30-min period of rest, and consequently exclude them from analysis, and (b) prevent participants from falling asleep, as sleep facilitates long-term memory processes (Born & Wilhelm, 2012; Dewald et al., 2010; Stickgold, 2005). Interestingly, many studies utilising an eyes-closed passive rest condition found significant enhancements to memory consolidation compared to an active rest condition (Brokaw et al., 2016; Dewar et al., 2012). Concurrently, some studies utilising an eyes-open passive rest condition failed to detect any enhancements in memory consolidation (Kuschpel et al., 2015). This raises the question of the possible differences in the mechanisms of effects between eyes-open and eyes-closed wakeful rest state. An fMRI study by Marx and colleagues (2004) showed differences in brain activation patterns between these two states and determined that the choice of rest state (eyes-open or eyes-closed) is essential for stimulus-induced brain activation patterns (Marx et al., 2004).

Before delving deeper into this line of research, it is important to reiterate that the consensus in the literature is that memory consolidation occurs on a synaptic level and systems level (Stickgold, 2005). However, the manner in which these processes occur is still not well known. Systems consolidation has been suggested to preferentially take place offline as the processes involved in the redistribution of memory representations to the long-term memory store may interfere with normal processing of external stimuli (Born & Wilhelm, 2012). Synaptic consolidation on the other hand is thought to equally occur during sleep and wakefulness (Born & Wilhelm, 2012). Previous to their aforementioned research in 2004, Marx and colleagues (2003) also found that ocular motor and attentional systems were activated during an eyes-open state (exteroceptive). By contrast, during an eyes-closed state, visual, somatosensory, vestibular, and auditory systems were activated (interoceptive), implying two different states of mental activity (Marx et al., 2003, 2004). Considering this distinction and the observation that the interoceptive eyes-closed state closely resembles REM sleep (during which the visual cortex is also activated and is also linked to synaptic memory consolidation (Igawa et al., 2001)), it is plausible that an eyes-closed state can elicit its memory-enhancing effects by mimicking certain aspects of sleep-associated processes for memory consolidation. Arguably, a deeper understanding of the pretext behind eyes-closed memory enhancement could derive from EEG data. This can be done by discerning differences in brain activity between eyes-closed and eyes-open wakeful rest and to then compare that to brain activity during sleep.

Active rest is meant to replicate typical daily periods of rest commonly filled with distractions such as listening to music, playing video games (Kuschpel et al., 2015), solving puzzles (Martini et al., 2018) or scrolling through social media on the phone or computer. In an experimental setting, distractor tasks bring about a form of interference that either contextually overlaps or is contextually distinct from the original memoranda (Varma et al., 2017). Additionally, many distractor tasks differ in cognitive demand, with some requiring a significant portion of the general resources available for cognitive processing and others requiring significantly less (Varma et al., 2017). All these factors could potentially play a significant role in influencing how active rest modulates memory consolidation. For example, Varma and colleagues (2017) highlighted that the majority of post-encoding distractor tasks show interference when compared to passive rest because the tasks typically contain complex and meaningful stimuli. This complexity requires a significant portion of the general resources available for cognitive processing and consequently results in interference. However, they also demonstrated that memory consolidation is not affected by a distractor task if the task has minimal semantic involvement and does not rely on hippocampally-based episodic memory processing (Varma et al., 2017).

1.3 High-intensity interval training

The literature suggests that a delay period between the onset of exercise and the cognitive memory task could support the effects of higher intensity physical exercise interventions (Chang et al., 2012). For example, Chang and colleagues (2012) found that high intensity physical exercise interventions negatively impacted memory performance when the cognitive memory task was performed immediately after or within a minimal delay period less than 10 min. Further, the authors found that this effect was reversed when the delay period was greater than 10 min (Chang et al., 2012). In another study, Hötting and colleagues (2016) demonstrated that participants in the high intensity physical exercise group (80% HR_{max}) forgot less words than the lower intensity group or rest group when the cognitive memory task was performed 24h after encoding (Hötting et al., 2016). By extrapolating the findings in the literature, it can be expected that due to the very high physical demand of high-intensity interval training (HIIT), potential enhancements on memory performance may be observed only after a significant delay between encoding and recall. This can be explained from previous literature showing longer physiological recovery rates after a bout of higher intensity exercise (75% maximal working capacity) compared to lower intensity (25 – 50% maximal working capacity) (Sjoberg, 1980). For example, even though physical workloads were matched between the physically "unfit" and "fit" group, the physically "unfit" group was not able to cope with the accumulation of the by-products that can negatively affect cognition (e.g. carbon dioxide and lactic acid) as well as the physically fit group (Sjoberg, 1980).

It is well documented that short bouts of HIIT and longer bouts of continuous exercise have considerably different neurophysiological effects (Astorino & Schubert, 2018; Ramos, Dalleck, Tjonna, Beetham, & Coombes, 2015; for review, Keating, Johnson, Mielke, & Coombes, 2017). Therefore, before Study 3 (Chapter 2) was run, a pilot study (*N* = 21) was run to equate the total energy expenditure consumed from the moderate-intensity physical exercise intervention and the HIIT intervention. This can be verified by looking at the data on Table 6 (study 3), which shows that mean energy expenditure (Joules) for moderate-intensity physical exercise was similar to that of HIIT, and yet HIIT maintained a considerably higher power (Watts). Furthermore, the HIIT protocol employed in this study was specifically designed to avoid participants entering anaerobiosis and suppress any possible detrimental effects of significantly high intensities of physical exercise that surpass the aerobic capacity (Rojas Vega et al., 2006; Wahl et al., 2010), bearing in mind the duration of the retention interval employed in this study. During the pilot study, participants completed a HIIT regimen that would exercise them to a self-reported RPE level between 17 – 20 , with energy output calculated and compared to the moderate-intensity physical exercise intervention. Four block of 30s HIIT resulted in a similar total energy expenditure as 2 blocks of 3 min moderate-intensity physical exercise (HIIT: $M_{expenditure} = 25.476$, $SD = 8.829$; Moderate-intensity physical exercise: $M_{expenditure} = 27.666$, $SD = 9.355$; $t(20) = 1.182$, $p = 0.251$). By matching the energy outputs and avoiding over anaerobiosis, any observable difference in performance accuracy scores between these two interventions would be less likely attributed to a difference in energy expenditure and more likely attributable to the intervention protocol.

The results obtained from Study 3 provide an interesting addition to the current literature on the impact that HIIT has on memory performance. Whilst the results showed a higher average performance score for HIIT (74%) compared to rest (71%), the difference between rest and HIIT were non-significant (p = 0.205). This result falls in line with the hypothesis and the current literature when considering the duration of the retention interval employed in this study. As previously mentioned, it seems that with high to very-high intensities of physical exercise, the longer the delay between the intervention and cognitive memory task, the better the memory performance score. This suggests that the timing in which the cognitive memory task (recall) is executed following physical exercise is key, as the consolidation of the stimuli is highly sensitive to external influences, such as those of a physiological (physical exercise) or psychological (cognitive engagement tasks) nature. To the best of my knowledge, this is the first study to have investigated the effects of post-encoding HIIT on long-term memory performance (now published Pyke & Ifram et al., 2020). That being said, a relatively recent study by Kao and colleagues (2018) investigated the immediate and delayed effects of pre-encoding HIIT on memory, and found that HIIT can enhance memory performance for both immediate and delayed recall tasks compared to rest (Kao et al., 2018).

Interestingly, however, whilst the findings in Study 3 show that HIIT generated non-significant increases in memory performance scores compared to rest ($p = 0.205$), these increases were also non-significantly different to the performance scores generated by moderate intensity physical exercise (77%) ($p = 0.130$). This goes against my hypothesis and this places the HIIT intervention in an intriguing position as it is neither significantly different from rest nor significantly different from moderate intensity physical exercise (which is significantly different to rest ($p = 0.011$)). Several factors should be considered here.

First, it is important to note that the HIIT intervention employed in this study differs from traditional HIIT protocols such as the one employed by Tabata and colleagues (1996), which is designed to surpass the aerobic capacity. As previously mentioned, the HIIT intervention employed in study 3 was designed to equate overall energy output between HIIT and moderate intensity physical exercise to ensure a neutral comparison between the two interventions. Had a traditional, more exhaustive HIIT protocol been employed for this study, the findings in the literature would predict that the performance scores would be significantly lower for HIIT relative to moderate-intensity physical exercise. Concurrently, given the high physical demand and relatively short delay between intervention and recall, the difference in performance scores between HIIT and passive rest may have remained non-significant, or even showed a HIIT-induced impairment in memory performance as not enough time would have elapsed for HIIT to positively modulate memory performance.

Second, given the relatively close overall performance scores on the old/new recognition task, the cognitive challenge of memorising the images may have been too easy and thus, performance may have been near peak potential across all interventions. By shortening the display time of each stimulus or increasing the number of to-be-remembered stimuli the cognitive challenge would be greater and larger differences in performance scores may have been observed.

Third, changing the type of cognitive memory task could also increase the cognitive challenge and result in greater differences in performance scores. Employing a free recall task instead of an old/new recognition task would further increase the cognitive challenge as the participants would no longer depend on retrieval cues. Therefore, it is likely that this change would lead to differences in memory performance that are more distinguishable between each intervention.

2. The effects of transcranial direct current stimulation on long-term memory

Over the course of three studies, the aims of chapter 3 were to (a) compare the effects of physical exercise and tDCS on long-term memory, (b) determine whether a combination of the two interventions can elicit further memory modulation, and (c) determine the effects on memory performance after a 24h retention interval period. Based on the results from the studies in chapter 2, the post-encoding moderate-intensity physical exercise protocol was selected for these studies as it yielded the highest average memory performance scores across all three studies. The tDCS protocol, adapted from previous research (Javadi & Walsh, 2012), was applied during encoding.

The studies in chapter 3 confirmed that moderate intensity physical exercise enhances long-term memory performance when tested 90 min after learning. However, when memory was tested 24h post encoding, performance scores after a bout of moderate intensity physical exercise were not significantly different to rest (control) (p = 0.393 after re-running analysis using d'). Additionally, whilst tDCS-induced long-term memory performance scores were not significantly different to that of moderate intensity physical exercise after 90 min retention (p = 0.672 after re-running analysis using d'), they were also not significantly different to rest (control) either (p = 0.082 after re-running analysis using d'),. Finally, although moderate intensity physical exercise and tDCS enhanced long-term memory as two independent interventions, combining them into one intervention had no effect on memory when test 90 min post encoding. Intriguingly, however, this combined intervention resulted in significantly lower performance score compared to control (p = 0.007 after re-running analysis using d').

2.1 Modulatory effects of transcranial direct current stimulation

It was hypothesised that anodal tDCS over the left DLPFC would yield comparable memory-enhancing effects on long-term memory as that of moderate intensity physical exercise. The results confirm this hypothesis: non-significantly different to physical exercise (p = 0.672 after re-running analysis using d'; confirming it is comparable to the effects of physical exercise). However, anodal tDCS was not statistically different to rest when significance was corrected for multiple comparisons (p = 0.082).

Many studies have demonstrated the positive memory-enhancing effects of anodal tDCS in both healthy and patient populations (Boggio et al., 2006; Javadi & Cheng, 2013; Javadi & Walsh, 2012; Jo et al., 2009; Santarnecchi et al., 2015). For example, Javadi and Walsh (2012) found that tDCS during encoding over the left DLPFC enhanced recognition memory. Also, Jo and colleagues (2009) demonstrated that anodal tDCS over the left DLPFC was associated with enhanced recognition memory. Similar to aforementioned studies, study 4 employed anodal tDCS over the left DLPFC.

Other factors may also play a role in determining the effects of tDCS on long-term memory. Stimulation duration over the left DLPFC may have been too short to allow for the full effect to take place. Other studies have shown that longer bouts of anodal stimulation enhance memory performance more than shorter bouts. For example, Ohn and colleagues (2008) demonstrated that tDCS over the left DLPFC resulted in significantly enhanced accuracy of response after 20 min, and was even further enhanced after 30 min. Conversely, however, a recent study has shown that increasing the duration of anodal stimulation does not necessarily enhance its efficacy (Hassanzahraee et al., 2020). Hassanzahraee and colleagues (2020) indicated that a threshold exists for anodal stimulation beyond 26 min, where a reversal of corticospinal excitability is seen. This finding is in line with another study that also found a reversal of anodal tDCS effects after 26 min (Monte-Silva et al., 2013). This reversal in effects has been attributed to the counter-regulatory, homeostatic mechanisms, described by the Bienenstock-Cooper-Munro rule (Bienenstock et al., 1982), which describes a dynamically sliding threshold of synaptic plasticity to keep neuronal activity within an optimal physiological range to prevent excessive excitation (LTP) or inhibition (LTD) (Hassanzahraee et al., 2020). Therefore, in the case of extended anodal tDCS, this counter-regulatory mechanism would prevent excessive brain activation by sliding towards LTD and reverse the excitatory effects of anodal tDCS on corticospinal excitability.

Current strength is another factor that may play a role in the efficacy of tDCS stimulation. Several studies found that increasing current intensity can enhance the efficacy of tDCS on memory performance. For example, Boggio and colleagues (2006) found that stimulation at 1 mA did not result in any significant performance change. However, stimulation at 2 mA resulted in significant enhancement in memory performance (Boggio et al., 2006). Whilst this finding is also supported by other studies (Teo et al., 2011), there is yet to be a systematic investigation into the effects of tDCS current strength on memory performance (Iyer et al., 2005).

2.2 Combined intervention of tDCS and physical exercise impairs memory

Across two studies (studies 5 and 6), the effects of a combined intervention of tDCS and physical exercise were investigated and compared to rest and physical exercise as an independent intervention at two timepoints (90 min and 24h post encoding). It was hypothesised that the combined intervention would yield a significantly higher performance score compared to physical exercise after 90 min and 24h. Additionally, compared to passive wakeful rest, it was hypothesised that the combined intervention would yield a significantly higher performance score compared to rest only after 90 min but have a comparable score when tested after 24h.

Contrary to the hypotheses, the combined intervention yielded a significantly lower performance score compared to physical exercise ($p = 0.007$ after re-running analysis using d’) and was no different to rest after 90 min ($p = 0.431$ after re-running analysis using d’). Additionally, and more intriguingly, results indicate that the combined intervention impaired memory performance after 24h as it yielded a significantly lower performance score compared to both the physical exercise ($p = 0.048$ after re-running analysis using d’) intervention and rest ($p = 0.007$ after re-running analysis using d’).

To my knowledge, this is the first set of studies that has investigated the effects of a combined intervention (physical exercise and tDCS) on long-term memory performance, as well as the temporal relationship of these effects on long-term memory performance.

Accordingly, the unexpected results of these studies have potentially opened up a new investigative path that may help to further elucidate the mechanisms involved in tDCS-induced- and physical-exercise-induced memory enhancement, and how their combination reverses these effects.

In chapter 3, two theories were introduced in an attempt to explain the observed impairment in memory performance following the combined intervention. First, I suggested that each protocol (tDCS, acute physical exercise) of the combined intervention may potentially compete for the same neural resources required to modulate long-term memory. For example, both anodal tDCS and acute physical exercise have been shown to enhance long-term memory performance by inducing excitatory cortical activity (Moraes et al., 2007; Nitsche et al., 2008). Therefore, given the limited neural and metabolic capacity of the brain (Chang et al., 2012), this competition may lead to diminished intervention-induced excitation as both protocols would be competing for the same, limited neural resources required to induce their modulatory effects on long-term memory; a sort of bottleneck effect (*Figure 24*). However, this would be more likely if tDCS, as an independent intervention, made the physical exercise task more difficult. If that were the case, this would mean that more neural resources would need to be allocated to the motor areas of the brain, thereby reducing the number of neural resources available for cognition.

Second, I suggested possible homeostatic mechanisms that may be triggered as a result of excessive brain activation following the combined intervention. These homeostatic mechanisms would, in this case, protect the homeostatic balance by reversing the intervention-induced mechanisms that would result in excessive excitation. This notion stems from the principles of negative feedback, which allows for various measures to be sustained within a specified range, as well as the aforementioned counter-regulatory measures described by the Bienenstock-Cooper-Munro rule. For example, it is known that tDCS induces lasting changes in cortical excitability beyond the end of stimulation, and that these changes are similar to LTP and LTD (M. A. Nitsche & Paulus, 2000). Additionally, Rotenberg and colleagues (2008) have demonstrated that in vitro anodal DCS in hippocampal slices potentiates excitatory post-synaptic potentials (EPSPs) and supports the notion that LTP-like mechanisms are involved in the physiologic changes induced by tDCS (Rotenberg et al., 2008). Animal research has shown that acute physical exercise facilitates LTP via several mechanisms, one of which is the potentiation of EPSPs in the hippocampus (Loprinzi et al., 2017). Therefore, it can be surmised that the combined intervention may introduce excessive potentiation of EPSPs, which may consequently trigger protective homeostatic mechanisms that would reverse the directionality of effects (Figure 25). This reversal may be achieved, for example, by releasing GABA, cortical neurotransmitter that inhibits neuronal excitability and used in inhibitory post-synaptic potentials (IPSPs).

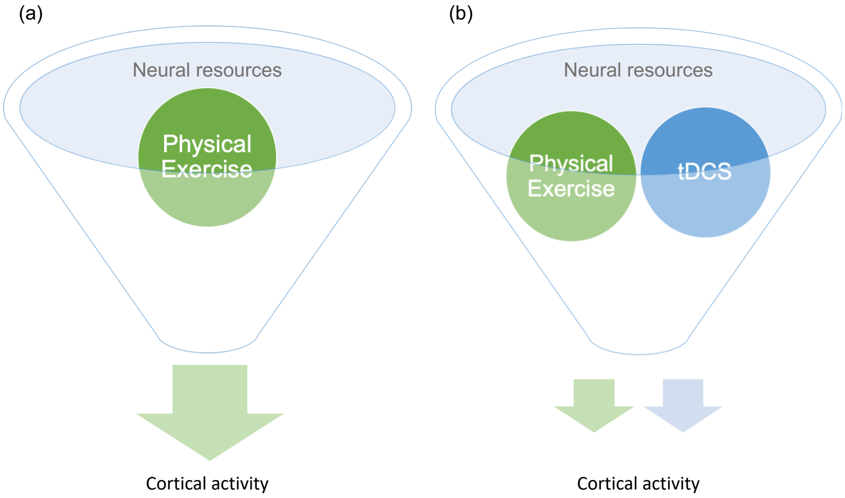
Another explanation for the diminished effects of the combined intervention of tDCS and physical exercise on long-term memory performance may be linked to NMDA-receptor antagonists. Previous studies have found dextromethorphan (DMO), an NMDA-receptor antagonist, to significantly suppress post-stimulation effects of tDCS (Madhavan & Shah, 2012; Michael A. Nitsche et al., 2003; Utz et al., 2010). Kynurenic acid (KA; an endogenous NMDA-receptor antagonist) expression has been shown to increase during physical exercise as a result of exercise-induced modulation of the kynurenine pathway (Joisten et al., 2020; Schlittler et al., 2016). Additionally, Mudry and colleagues found that acute exercise directly affects circulating levels of kynurenine and KA (Mudry et al., 2016). Given that KA is an NMDA-receptor antagonist, it can be assumed that KA might have similar negative post-stimulation tDCS effects to that of DMO. Therefore, by combining tDCS and physical exercise, it is plausible that the exercise-induced release of KA may suppress the effects of tDCS. It is important to note, however, that knowledge about the impact of acute physical exercise modalities on the kynurenine pathway is limited and only recently have studies began to delve into this area of research (Joisten et al., 2020).

Previous studies have shown that tDCS over the motor cortex can have positive ergogenic effects on physical exercise performance, particularly a lower RPE, improved maximal power output, reduced perception of pain, as well as improved cycling time to exhaustion (for review: Angius et al., 2017). These positive ergogenic effects could also impact the intensity a participant is working at (participants might feel the prescribed intensity to be easier than a control (no tDCS). Although the balance of evidence suggests an overall positive effect of tDCS (over the M1 motor cortex) on exercise capacity, the results have nevertheless been inconsistent (Angius et al., 2017). It is plausible that some of these ergogenic effects may be replicated when stimulating the left DLPFC, of which the perceived physical exercise intensity is of importance as it was something that I was trying to control throughout the studies. However, on the basis of the findings in the studies of this thesis, alongside the pivotal role of the motor regions of the brain in the development of supraspinal fatigue (exercise-induced decline in force as a result of suboptimal output from the motor cortex) via changes in motor cortex excitability (Angius et al., 2017), it seems that the ergogenic effects as a result of tDCS are specific to motor cortex stimulation. That being said, further research is required to support this statement, and as such, should be approached with caution.

Study 6 was originally designed as a within-subject study. However, due to a change in the RPS credit scheme across the School of Psychology, which implemented a new cap on the maximum number of credits allowed to be rewarded per term per study, Study 6 adopted a between-subject design. This change in study design, whilst necessary, prevented direct comparisons of memory performance between each intervention group per participant as the required time for a participant to complete all three interventions would exceed the maximum permitted credits.

Figure 24.

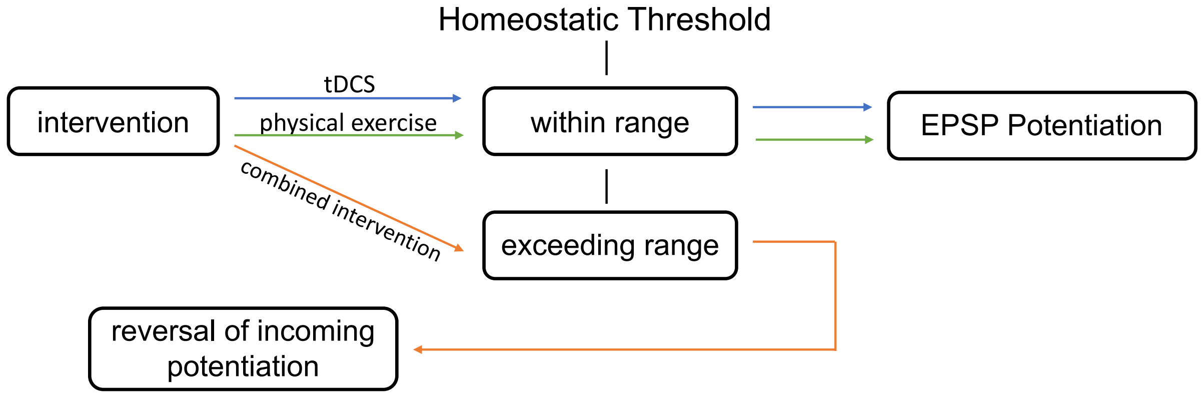
Competition for the same neural resources.



Note: This is a schematic representation of one of the proposed theories for the negative effects observed when using a combined intervention. (a) Acute physical exercise as an individual protocol, unhindered by a competing protocol, could use as much of the available neural resources as required to elicit its increases in cortical activity, subsequently leading to long-term memory enhancements. (b) Using a combined intervention, each protocol competes for the limited availability of neural resources. This, consequently, may diminish the efficacy of both protocols at enhancing long-term memory performance.

Figure 25.

Homeostatic mechanism to prevent excessive activation.



Note: This is a schematic representation of one of the proposed theories for the negative effects observed when using a combined intervention. tDCS and acute physical exercise as independent interventions have been shown to enhance memory performance via several mechanisms, for example, the potentiation of excitatory post-synaptic potentials (EPSP). As independent interventions, the incoming intervention-induced excitation may be within the predetermined homeostatic range, which would not prompt homeostatic control. The combined intervention, however, may elicit incoming intervention-induced excitation that exceeds the homeostatic range. Consequently, this would trigger homeostatic control in order to protect the homeostatic balance by reversing the intervention-induced mechanisms that would result in excessive excitation.

After a retention interval of 24h, the physical exercise intervention, which employed a moderate intensity, did not produce significant enhancements in long-term memory performance compared to rest. Previous literature suggest that this may be due to the intensity of the physical exercise protocol. Hötting and colleagues (2016) found that when memory was tested 24h post encoding, only the participants in the high-intensity physical exercise group (compared to the submaximal intensity group) forgot less words than the participants in the resting group (Hötting et al., 2016).

Results indicate that the combined intervention significantly impairs memory performance 24h post encoding. Whilst direct comparisons between Study 5 and Study 6 cannot be drawn (due to different study design and cohort of participants), preliminary findings suggest that after a 24h retention interval, the efficacy of the combined intervention diminished from 64.2% to 51.9%. This is similar to the diminished efficacy observed for the physical exercise intervention after 24h, which dropped from 69.7% to 57.8%. Interestingly, however, for passive wakeful rest/control, memory performance was seemingly maintained (increase of 1%) after 24h. This may suggest a possible delayed effect of rest on long-term memory. For example, results from Study 6, without the framework from previous studies (particularly study 5), indicate that passive wakeful rest enhances long-term memory performance as much as acute, moderate-intensity physical exercise over a 24h period. Whilst this may indeed be true, it is important to consider that the data from studies 2 – 5 indicate no enhancing effect of wakeful rest on long-term memory (after 90 min). In turn, taken together with the aforementioned preliminary findings, it can be argued that passive wakeful rest may not directly enhance long-term memory performance after 24h, but instead, is able to maintain memory performance (i.e. reduced forgetting) for at least that given period of time. A study by Mercer (2015) found that a brief period of wakeful rest before completing a distractor task helped reduce the amount of forgetting (Mercer, 2015). On that basis, it is plausible that the physical exercise and combined interventions may have inadvertently acted as distractor tasks, which may account for the observed diminished efficacy after 24h compared to passive wakeful rest.

3. Neural oscillatory activity during physical exercise

In addition to investigating the behavioural effects of acute, moderate-intensity physical exercise on long-term memory performance, I wanted to investigate the correlation between neural oscillatory activity during physical exercise and enhanced long-term memory. Whilst neural oscillatory activity across the frequency bands has repeatedly been linked to encoding and retrieval, investigations into the neural correlates of EEG with long-term memory performance during acute physical exercise have been greatly ignored. This was achieved by recording EEG activity during the physical exercise sessions of study 2. Results indicate significant positive correlations across all frequency bands except alpha, which yielded a significant negative correlation with enhanced long-term memory.

3.1 Theta oscillatory activity

Significant prefrontal and frontal activity were predominantly occupied by theta band oscillations (4 – 7 Hz). This is in line with the literature, which has previously shown positive correlation and phase synchronisation of theta band oscillations in frontal regions of the brain (Klimesch, 1999; Nyhus & Curran, 2010). Furthermore, in their review, Nyhus and Curran (2010) found that theta phase synchronisation between frontal and posterior regions of the brain modulate retrieval of declarative memories. The results of study 2 also fit well with these findings as significant theta band oscillations were correspondingly detected in the centroparietal region of the brain, which further corroborates the role of theta band oscillations for enhanced long-term memory performance.

Theta oscillations have previously been observed in the prefrontal cortex and are a strong, predominant component of prefrontal cortex-hippocampal interactions (for review: Benchenane et al., 2011). Moreover, this interaction via theta oscillation is involved in long-term memory storage, where relevant information is selectively chosen to be stored (Benchenane et al., 2010, 2011).

3.2 Alpha oscillatory activity

Significant alpha band oscillations were detected in a cluster around the central electrodes. Alpha band oscillations were negatively correlated with memory performance and this is supported by the literature, which, as mentioned above, suggests that alpha activity responds in the opposite direction to theta (Klimesch, 1999; Nyhus & Curran, 2010) and engages the thalamo-cortical network (located centrally; engages the somatosensory cortex; would appear on the same electrodes that detected alpha activity) (Klimesch, 1999; Klimesch et al., 2008; Klimesch et al., 1997). Furthermore, Düzel and colleagues found alpha desynchronisation during responses to an old/new recognition task where the stimuli were visually presented words (Düzel et al., 2003). This is similar to the cognitive task used in study 2.

Klimesch and colleagues (2005) reported that neural oscillations of different frequencies are best coupled if their frequency relation follows a 1:2 ratio (Klimesch et al., 2005). Of interest, therefore, is the link between theta (4 – 7 Hz) and upper alpha oscillations (10 – 13 Hz). This suggests that theta and upper alpha oscillations are co-activated and exhibit phase-coupling. The authors surmised that the best example is that theta wave oscillations exhibit phase synchronisation, whereas upper alpha oscillations exhibit desynchronisation and the timeframe of co-activation is short and limited to evoked activity, such as the presentation of a stimulus (Klimesch et al., 2005). Previous to this study, the same authors (Sauseng et al., 2002) investigated the interplay between the working memory system and long-term memory system. This was achieved by analysing evoked theta and upper alpha desynchronisation in a specialised memory task designed to investigate information transfer between the two systems (Sauseng et al., 2002). Similar to the later reported findings in the review by Nyhus and Curran (2010), Sauseng and colleagues found that evoked theta band oscillations spread from frontal to posterior regions of the brain. Further, they report that this spread from the anterior to posterior is reversed when information is retrieved and is strongly correlated with memory performance and the onset of upper alpha desynchronisation; reflecting the transfer of information between the two memory systems (Sauseng et al., 2002). These findings further support the findings of study 2 showing theta wave synchronisation and alpha wave desynchronisation for enhanced long-term memory.

Whilst many studies show a correlation between alpha wave desynchronisation and enhanced long-term memory, a few studies have demonstrated the opposite. For example, Khader and colleagues (2010) found increased alpha power during working memory maintenance for successfully remembered stimuli and suggested that this reflects successful long-term memory encoding. The authors posited that, since successful encoding involves processes similar to those invoked by increasing working memory load, successful long-term memory encoding could be associated to working memory activity (Khader et al., 2010). However, the authors conceded that this notion contradicts many previous findings linking alpha desynchronisation to successful long-term memory encoding.

3.3 Beta oscillatory activity

Beta band oscillations were primarily located in the frontal region and positively correlated with long-term memory performance, except for the beta oscillations detected on one parietal electrode (P3), which was negatively correlated. In contrast, the literature indicates a negative correlation between beta band oscillations and memory performance

(Guderian et al., 2009; Hanslmayr et al., 2012), especially for semantic memory (Fellner et al., 2013). Other studies have also shown decreased beta power subsequently remembered items in the lateral regions of the left and right temporal lobes (Hanslmayer et al., 2009; Sederberg et al., 2007).

Hanslmayr and colleagues (2012) found significant beta power decreases (accompanied by alpha power decreases) during encoding for words that are subsequently remembered compared to words which are forgotten (Hanslmayer et al., 2012). Additionally, in another study, Hanslmayr and colleagues (2014) found that prefrontal cortex stimulation at the task-relevant beta frequency interfered with memory encoding and concluded that beta desynchronisation is more than a by-product, but instead, plays a pivotal role for memory formation (Hanslmayr et al., 2014). Importantly, other studies (Burgess & Gruzelier, 2000; Düzel et al., 2003; Spitzer et al., 2009) found strong beta power decreases in successful memory retrieval as well.

Of special interest, is the study by Burgess & Gruzelier (2000), which found that the recall of words induced stronger beta power decreases over the left parietal electrodes compared to faces, which induced stronger power decreases on the right parietal electrodes. This finding complements the negatively correlated beta oscillations detected at the P3 electrode (Figure 20). Furthermore, by incorporating two concepts, the findings of study 2 regarding beta oscillations can be further elucidated.

First, as described by Niedermeyer (1999), beta oscillations can be categorised based on their topography: frontal, central, posterior, and diffuse beta. Specifically, frontal beta rhythms were reported to consist of faster beta frequencies (>20 Hz), whereas posterior beta rhythms were described as the equivalent to fast alpha rhythms (>10 Hz) (Niedermeyer, 1999). Second, as mentioned previously, alpha band oscillations are negatively correlated with enhanced memory performance (Klimesch et al., 2005; Nyhus & Curran, 2010; Sauseng et al., 2002). Therefore, given that posterior beta rhythms have been equated to fast alpha rhythms, which have been associated to enhanced long-term memory performance through desynchronisation, it can be argued that the significant beta activity detected at P3 (Figure 20) is within the lower beta frequency range (~13 Hz), and thus, verify the findings. Finally, given the relatively indistinct frequency band range (for example, beta band frequency has been reported at: 13 – 30 Hz: Braun et al., 2017; 8 – 30 Hz: Hanslmayr et al., 2012; 15 – 25 Hz: Kirov et al., 2009) it is possible that the significant beta oscillations detected at P3 may in fact be fast alpha oscillations.

Beta oscillations in the frontal electrodes, however, demonstrated a positive correlation with memory performance. Whilst this goes against the findings in the literature, which indicate a negative correlation, there is a possible explanation for this outcome. Frontal beta activity has previously been shown to be associated with motivation and relative evaluation of reward values (Cohen et al., 2007; Kawasaki & Yamaguchi, 2013; Marco-Pallares et al., 2008). Kawasaki & Yamaguchi (2013) detected this frontal reward-related beta activity at 24 Hz, which is in line with Niedermeyer's (1999) statement that frontal beta rhythms consist of faster beta frequencies. Kawasaki & Yamaguchi (2013) concluded that the frontal reward-related beta activity is integral in facilitating increases in visual working memory capacity. Although the EEG data that was used was extracted from the short rest periods of the physical exercise intervention, participants in study 2 were required to continuously monitor their cadence within the allocated cadence bracket by actively looking at the cycle ergometer screen. By default, this would engage the working memory system as participants would look at the screen and decide whether to maintain, increase, or decrease cadence as set by the allocated cadence bracket.

3.4 Gamma oscillatory activity

Increased gamma oscillations play a crucial role in attention as well as the encoding of long-term memories, demonstrated via neural synchronisation of memory representations in the areas of the brain that receive and process sensory information (Jensen et al., 2007). Furthermore, increased recall of items has been ascribed to increased gamma oscillations in the occipital areas (Jensen et al., 2007; Osipova et al., 2006).

Friese and colleagues (2013) found increased gamma band oscillations in parietal regions of the brain during encoding of visual stimuli of which participants later successfully remembered (Friese et al., 2013). This effect, of significantly greater activation of a particular brain region during encoding of which later retrieval is successful, is known as a subsequent memory effect (SME) (Rypma & D'Esposito, 2003). Simultaneous to the increased gamma oscillations, the authors identified sources in the right frontal cortex for theta band SME and concluded that successful encoding was represented by theta activity in the right frontal cortex as well as gamma activity in parietal regions (Friese et al., 2013). In some measure, the observed gamma oscillations detected in study 2 fall in line with these findings since the majority of significant gamma oscillations were detected in the posterior region of the brain, and significant theta activity was also detected in the right frontal cortex (Fp2, AF4, F4, F6). Although no significant gamma oscillations were detected in the occipital areas post-FDR correction, increased gamma oscillations and enhanced memory performance at the PO9 electrode was approaching significance (Figure 22). In their review, Nyhus and Curran (2010) detail the relationship between gamma and theta oscillations in episodic memory and state that these oscillations allow for successful encoding and retrieval via transient interactions between cortical structures and the hippocampus. The perceptual and contextual information from several brain areas are bound into episodic representations via gamma wave synchronisation and these representations are temporally ordered by theta oscillations (Nyhus & Curran, 2010). This confirms the aforementioned findings (Friese et al., 2013; Jensen et al., 2007; Osipova et al., 2006) and also supports the findings in study 2 regarding gamma and theta band oscillations.

It is important to reiterate that, whilst the majority of previous literature indicate correlations of oscillatory activity with enhanced memory performance, these correlations were determined either during encoding or recall. The EEG findings in study 2 are based on correlations between neural oscillatory activity *during* post-encoding physical exercise and enhanced long-term memory. As such, it is important to continue with this line of research and determine oscillatory activity during a controlled consolidation period (e.g. no intervention; rest) and compare the modulatory effects on neural oscillatory activity during consolidation.

4. Research limitations and future directions

Calculating the power of a study enables the detection of an effect when there is an effect to be detected. It is the ability for a study to demonstrate a causal relationship between two variables. By and large, this is dependent on the size of the effect (Cohen's *d*) because large effects are more easily detected and consequently increase the power of a study. The power of a study also acts as a measure for a study to avoid Type II errors. When a study has a small sample size, chances of Type II errors are increased, which can lead to results being skewed, thereby decreasing the power of a study. For example, a study with 0.85 power indicates an 85% chance of $p < 0.05$ between two variables. In contrast, a low power would indicate that the study was too small to detect any differences and the results could be disputed.

It is generally accepted that a power for a study should be 0.8 or greater. Studies 1 – 6 were generally underpowered, where statistical power was below 0.8. This could explain some of the variability of the observed effects, particularly for moderate-intensity physical exercise, which was performed consistently throughout the studies. For example, to achieve a power > 0.9 to detect an effect size of Cohen's $d = 0.8$, at two-tailed $\alpha = 0.05$, total sample size would have to be 68 (34 per group), demonstrating a considerably smaller achieved sample size for each of the studies. The final sample size was reduced due to several factors including missed attendance, exclusions due to low performance on the memory task, or participants reporting a score of 4 or more on the Stanford Sleepiness Scale. One considerable implication of underpowered studies is that they can produce false-positive results, or overestimate the magnitude of association (Hackshaw, 2008). Therefore, whilst I have reported significant memory performance enhancements as a result of moderate-intensity physical exercise compared to other intensities as well as rest, these findings need to be interpreted carefully.

Intriguingly, studies 1 – 4 recorded memory performance scores of at least 70% accuracy. This overall high performance score could indicate that the memory task was not challenging enough. Therefore, future research may benefit from increasing the difficulty of the encoding task, which could potentially accentuate differences in memory performance between intervention groups, and also, potentially increase statistical significance. That being said, the potential avenues for increasing the difficulty may be limited. For example, all the studies in this thesis displayed each stimulus for 1s during encoding. Therefore, reducing the duration of stimulus presentation may not be a suitable route as this may lead to missed stimuli, for example, as a result of participants briefly gazing elsewhere. As such, it may be more beneficial to either increase the number of stimuli presented during encoding (e.g. from

80 to 120 images), or to reduce the presentation duration of the fixation cross that appears between each image from 2s to 1s. Furthermore, where recognition tasks offer specific recognition cues, free recall tasks require access to specific information in memory with far fewer cues to retrieve said information, making it more challenging for participants (Rhodes et al., 2019). Therefore, it may be of interest to employ a free recall task and compare those findings to the findings in studies 1 – 6.

Across all studies, there was some variability in the effects of moderate-intensity physical exercise. For example, in Study 3, moderate-intensity PE yielded significantly better performance accuracy scores compared to passive rest ($p = 0.011$), whereas in Study 2, this comparison was not significant ($p = 0.055$). This variability can be attributed to several factors. First, as previously discussed, the small sample size may have affected the results. Second, environmental factors have to be taken into account. Due to lab booking availability, not all sessions were run in the same lab. Some sessions were run in the EEG lab (relatively small, well ventilated, and relatively quiet to external noise), other sessions were run in a larger study room (well ventilated, quiet, but subject to possible disturbances from students entering the room by mistake), and finally some sessions were run in a very large room with similar conditions to the study room. Additionally, these studies were not all run within close proximity to each other. The data for Studies 1 – 6 were collected across three years, and therefore, included different cohorts of students. Also, whilst all condition orders were randomised, it is important to iterate that the data was checked to determine whether there were any significant differences between participants that performed the control condition on the first session or participants that performed the control session on the second or third session: no differences were found.

The variability of effects of moderate-intensity physical exercise may also be linked to how exercise intensity was defined. To determine physical exercise intensity bands, I used %HR_{max}. However, using this method might cause some intra-individual variability for crossing important thresholds. Coakley and Passfield discuss some of these variabilities when exercise intensity is set to a standardised maximum physiological characteristic such as %VO_{2max} or %HR_{max} (Coakley & Passfield, 2018). This includes individual variability in %VO_{2max} adaptations ranging from no change to approximately 42% increase (Bouchard et al., 1999), as well as inter-individual variabilities in time-to-exhaustion (Coakley & Passfield, 2018). Many of these variabilities are typically ignored by researchers when setting physical exercise interventions. However, a study by Coakley & Passfield aimed to account for this by tailoring the duration of training to each participant's maximum performance time (100% of pre-training time-to-exhaustion) rather than a set time with a set %VO_{2max} or %HR_{max}. Additionally, exercise intensities were defined based on each participant's power output at VO_{2max} (MAP), where moderate-intensity was set at 60% MAP in blocks of 5 min with 1 min recovery, and high-intensity at 100% MAP in blocks of 2 min with 3 min recovery. Coakley & Passfield report approximately 80% less time spent training for high-intensity exercise intervention compared to the moderate-intensity intervention and approximately 63% less compared to a mixed intervention of high and moderate intensity (Coakley & Passfield, 2018). However, despite significantly greater time spent training at moderate-intensity, performance and physiological adaptations were similar across the training intensities.

Other studies have reported that by prescribing a set %VO_{2max} or %HR_{max} variability in metabolic thresholds will arise because, for example, 70% HR_{max} for some participants may be above or below certain metabolic thresholds, including the aerobic and anaerobic thresholds (Mann et al., 2013). This may account for some of the variability observed in the outcomes to physical exercise seen in Studies 1 – 6. For example, by setting an HR_{max} at 55 – 65%, for some participants this may be within the aerobic threshold, but for other participants this $\%HR_{max}$ may be too high and cross into the anaerobic threshold.

Laursen reported that training at one exercise intensity will only activate training adaptations specific to that intensity, and in order for other adaptations to occur, training should be mixed with different intensities (Laursen, 2010). This mixing of intensities has been shown to lead to increases in physiological and performance adaptations (Coakley & Passfield, 2018; Laursen, 2010). Therefore, future research would benefit greatly by taking these into consideration. For example, by setting an exercise protocol where (a) exercise intensity is based on a participant's MAP (Coakley & Passfield, 2018), (b) the duration of that protocol being determined by each participant's maximum performance time (Coakley & Passfield, 2018), and (c) introducing a mix of high and moderate intensities into the exercise protocol to elicit increases in physiological adaptations (Laursen, 2010), we would be able to better observe and elucidate the effects of physical exercise on long-term memory and, importantly, have well defined boundaries of physical exercise intensities.

Similarly, some inconsistencies in performance accuracy scores for passive rest were observed across the studies. Performance accuracy scores for passive rest in Studies 2 – 4 ranged between 71.46 – 77.79%, whereas performance accuracy scores for passive rest in Studies 5 and 6 were considerably lower at 61.39 – 62.23%. In addition to the aforementioned environmental factors, Studies 5 and 6 were run towards the end of the Research Participation Scheme, and generally, the remaining available participants are rushing to obtain the necessary credits to complete the academic year. Researchers from previous years and different studies have indicated that overall participant engagement in studies during this time period is considerably lower than normal. This may have impacted and contributed to the inconsistent performance scores for passive rest (as well as for all conditions) across Studies 1 – 6.

Future research should also investigate the effects of acute physical exercise, tDCS, and combined interventions on different age groups, particularly older adults, and neurodegenerative patient populations. This will not only aid in elucidating how these intervention effects differ by age but will also help in interpreting how these interventions may best be used in patient populations to delay onset of dementia and perhaps produce a treatment plan to slow the rate of cognitive decline.

Whilst acute, moderate-intensity physical exercise has clearly demonstrated significant long-term memory enhancements when test after 90 min, several studies have demonstrated better memory performance after 24h using higher intensities of physical exercise compared to moderate intensities (Hötting et al., 2016). Further, given that physical exercise in study 6 produced a performance score no different to rest after 24h, it would be beneficial to test whether higher intensities of acute physical exercise can consolidate long-term memory better over longer periods, such as 24h and 7 days.

Following this train of thought, future research should investigate the effects of post-encoding HIIT on long-term memory performance. More specifically, a typical HIIT protocol should be employed rather than the protocol used in study 3. In study 3, a specifically designed protocol was employed so that participants were not over exhausted, and particularly so that they were less likely to enter a state of anaerobic exercise. Instead, the protocol was designed to equate the total energy expenditure consumed from the moderate-intensity physical exercise intervention and the HIIT intervention. By matching the energy outputs and avoiding over exhaustion, any observable difference in performance scores between the two interventions would be less likely attributed to a difference in energy expenditure and more likely attributed to the intervention protocol i.e. a continuous physical exercise intervention vs. an exercise intervention interspersed with rest period. Using a traditional HIIT protocol would lead to participant exhaustion and, subsequently, enter a state of anaerobic exercise. This would allow for the comparison in memory performance of aerobic exercise to anaerobic exercise.

For the low-, moderate-, and high-intensity physical exercise interventions, a range of different cadences were used (60 – 70, 65 – 75, 70 – 80 rpm). This was done to avoid any confound of a fixed cadence. With a fixed cadence it would be difficult to conclude that any outcome observed from the EEG analysis was not a result of a specific cadence. Furthermore, using different cadences kept participants focused on the cycling task and limited mind-wandering as they had to monitor the set cadence displayed on the monitor. This also kept participants heads facing forward and focused on the monitor, which aided in obtaining cleaner EEG recordings as it limited head movement. The selected cadences were specifically chosen to be under 100 rpm in order to avoid (or at least prolong) the onset of anaerobiosis. Zoladz and colleagues demonstrated that pedalling over 100 rpm reduced delivered the power output at any given oxygen cost, which led to the earlier onset of anaerobiosis (Zoladz et al., 2000). Furthermore, as demonstrated by Takaishi and colleagues (Takaishi et al., 1996, 1998), lower cadences of around 60 – 70 rpm are associated with minimised muscular fatigue and reduced oxygen consumption, thereby providing the participants with a greater likelihood of remaining in aerobiosis (Abbiss et al., 2009).

However, whilst beneficial for the aforementioned reasons, this does come with some limitations. Different cadences can present different physiological effects. For example, in their review, Abbiss, Peiffer and Laursen (2009) state that higher cadences (100 – 120 rpm) reduce muscle force and neuromuscular fatigue, and consequently maximise cycling power output compared to lower cadences, whilst lower cadences (70 – 90 rpm) improve cycling economy and lower energy demands. However, such low cadences are known to increase pedal forces required for the maintenance of a given power output (Abbiss et al., 2009). Several studies (for review: Abbiss et al., 2009) have sought to define the optimal cycling cadence, however, to date this remains unclear. It has been postulated that this uncertainty in finding the optimal cadences may be due to methodological inconsistencies between studies, as well as trying to define the term "optimal" in this instance (Abbiss et al., 2009). For example, an optimal cadence for the most comfortable pedal rates will be different to an optimal cadence for the most economical pedal rates.

As part of these studies, EEG was recorded during physical exercise to investigate correlations between neural oscillations and enhanced memory performance. However, in order to record EEG accurately, the 30 min exercise interventions had to be split into six bouts of 4 min cycling and 1 min rest, where the EEG data during the 1 min rest was used for analysis. Without this 1 min rest period, the EEG recording would have been too noisy to analyse due to the movement caused by cycling. However, physical exercise intensities in these studies were standardised based on % of maximum heart rate (HR_{max}) with the additional aid of the Borg Rating of Perceived Exertion Scale (RPE) tested after each bout (Borg, 1982), therefore, by splitting the 30 min exercise interventions into six bouts, other variables come into play. In particular, the time it takes for a participant's heart rate to reach the designated range of HR_{max} in order for the exercise intervention to be classified as a specific intensity. For example, after each exercise bout, the participants heart rate would drop (during the 1 min rest) and would take between 30 s – 1 min to reach the desired heart rate and stabilise at that range for the next exercise bout. Therefore, it could take up to 25%

of the allocated exercise time for a participant's heart rate to reach the desired range, which may considerably affect the results.

For example, given that the continuous 30 min exercise interventions was split into six bouts to aid EEG recording, total exercise time was reduced to 24 min. Additionally, factoring in up to 6 min (1 min per bout) for heart rate to reach the $\%HR_{max}$ threshold, exercise time is further reduced to 18 min. Petruzzello and colleagues found that at least 20 min of physical exercise is required for physiological effects such as a reduction in state and trait anxiety to be observed (Petruzzello et al., 1991). Furthermore, Labban and Etnier demonstrated that after 30 min of continuous moderate-intensity exercise, participants outperformed the control group (Labban & Etnier, 2011). Future research which requires the recording of EEG during exercise should address these limitations by adding additional exercise bouts to make up for the lost time (both in the time it takes for the heart rate to reach the specified threshold and the time lost during the 1 min rest for each exercise bout). Furthermore, if EEG data is not required, future research would benefit from testing whether these bouts affect memory performance compared to an exercise protocol made of one single bout of 30 min of continuous exercise.

There is a distinctive brain wave known as the sensorimotor rhythm (SMR), which is an idle rhythm that oscillates at a frequency range of 12 – 15 Hz over the sensorimotor cortex. It typically synchronises during quiet but alert wakefulness and decreases during planning, execution and imagination of body movements (Hoedlmoser et al., 2008). SMR rhythms are occasionally mixed up with stronger sources of upper alpha rhythms (likely due to inappropriate spatial filtering). However, significant, negatively correlated oscillations were detected in the 12 – 15 Hz range during physical exercise (Figure 23). This falls in line with previous research demonstrating SMR desynchronisation during movement (Kübler &

Mattia, 2015). Therefore, it would be of interest to investigate the correlation between neural oscillatory activity during passive/active wakeful rest and enhanced long-term memory, particularly SMR oscillations during passive rest, where participants are at their most quiet and idle state.

Additionally, whilst EEG was analysed on a single electrode basis, another option would have been to analyse the EEG data in regions of interest. For the purposes of this thesis, looking at individual electrodes provides more detail and a clearer image of what is going on and gives a better understanding for targeting specific brain areas. For example, with enhancements in brain stimulation technologies more precise targeting of cortical structures is now possible using HD-tDCS compared to conventional tDCS devices. HD-tDCS allows for better focality and for unifocal stimulation, which is in contrast to conventional tDCS devices that require one anode and one cathode, always producing bidirectional modulation (Datta et al., 2009). Therefore, by analysing the EEG data on a single electrode basis, it allows to more precisely observe which cluster of electrodes are implicated and, subsequently, allow for future research to target that cluster (e.g. by using HD-tDCS).

Finally, tDCS research comes with some complications with regards to electrode montage. Many studies that claim to stimulate the same site do so with different electrode positioning (Karabanov et al., 2019; for review: Radecke et al., 2019). Bestmann and colleagues describe that in order for the effects of transcranial electrical stimulation to be established with confidence, combined computational, physiological, and behavioural models are needed (Bestmann et al., 2015). Current flow models, which involve segmenting MRI images into different tissue types, are used to confirm if an electrode montage is stimulating the targeted brain area (e.g. left DLPFC). Current flow models have previously been used in tDCS studies targeting the left DLPFC (Bonaiuto et al., 2016). Due to the lack of an MRI machine at the University of Kent and a very limited budget, current flow modelling was not performed for the tDCS studies, which means that one cannot establish with confidence that the stimulated brain area was in fact the left DLPFC. Therefore, future research would benefit from a collaboration with another university or hospital with an MRI machine to allow for current flow modelling.

5. Implications

This research tested the effects of different intensities of physical exercise and has shown that post-encoding moderate-intensity yields the greatest enhancements long-term memory performance. This finding could have significant implications in an educational setting, particularly in primary and secondary education, where physical exercise is incorporated into the curriculum (PE classes). This finding, along with future research on the effects of the type of physical exercise on memory, could influence which sports to focus on in PE classes and how much physical exertion is needed. Further, it could also determine the scheduling of PE classes. For example, by avoiding PE classes first thing in the morning (pre-encoding), and instead schedule the classes just before lunch (post-encoding), where it is typically a post-encoding period free of retroactive interference (Martini et al., 2017; McDevitt et al., 2014; Mercer, 2015; Stickgold, 2005).

Physical exercise has also been shown to be beneficial in older adults and for the treatment of patients with memory deficiencies. With regards to the latter, especially patients placed in care homes, incorporating an appropriate physical exercise regimen could slow down the rate of cognitive decline. However, some patients (as well as children, adults, and older adults) may not be able to be physically active and would, therefore, benefit from another regimen. This thesis demonstrated the positive effects of anodal tDCS on long-term memory, which could be used as a substitute for physical exercise in such situations. Whilst many studies have shown beneficial effects of tDCS on long-term memory, the application of tDCS in a clinical setting typically requires repeated hospital visits, with its benefits in a clinical setting being quite limited (Park et al., 2019). As such, the use of tDCS devices at home has been gaining traction. For example, Flow Neuroscience have recently developed an at-home tDCS device that is easy to use and relatively inexpensive, with studies supporting its beneficial claims (Borrione et al., 2020). Although, this device is in fact used for the treatment of depression, similar at-home devices could be made that target memory performance. The findings in this thesis, along with future research, could aid in determining an appropriate schedule and protocol for using tDCS at home to enhance memory performance.

Importantly, this thesis demonstrated that a combination of physical exercise and tDCS impairs memory performance and should not be used together. This finding sheds light on the antagonistic interaction between the two interventions and could serve as a caution for cognitive therapies implementing physical exercise or electrical brain stimulation. Further research will be needed to verify and expand on this finding.

Finally, this thesis has shown that short periods of post-encoding uninterrupted wakeful rest increases the likelihood of remembering at a later date. Producing clear guidelines for long-term memory enhancement that covers the variability in the literature could have significant implications in the treatment of patients with memory deficiencies, as well as in the normal population, including students in an educational setting.

6. Conclusion

Through a series of six studies, this thesis explored the modulatory effects of physical exercise and transcranial direct current stimulation on long-term memory. Concurrently, EEG was recorded during physical exercise to investigate the correlations between neural oscillatory activity and enhanced long-term memory performance. These studies demonstrated that acute, moderate-intensity physical exercise significantly enhanced long-term memory performance compared to lower- and higher intensities. Additionally, moderate-intensity physical exercise significantly enhanced long-term memory performance compared to wakeful rest (active and passive) when tested on the same day, however, when tested after 24h, moderate-intensity physical exercise is no different to passive rest.

These studies also revealed that tDCS produced comparable performance scores to those achieved by acute, moderate-intensity physical exercise. For the first time, it was shown that the combination tDCS and physical exercise as one intervention impairs long-term memory performance, especially when tested 24h post encoding. Finally, significant correlations between neural oscillatory activity and enhanced long-term memory performance were found during physical exercise. Negative correlations between alpha and parietal beta oscillations were linked to successful long-term memory enhancement, whereas positive correlations between theta, gamma, and frontal beta were associated with successful long-term memory enhancement.

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Appendix

The effect of different intensities of acute, physical exercise, and active wakeful rest on BDNF concentration

As previously mentioned in section 3 of the discussion, due to the unforeseen circumstance of the freezer breaking down at the University of Kent Medway campus, all the collected saliva samples from studies 1 and 2 were rendered perished. Saliva samples were collected at three timepoints (before intervention, after intervention, and after old/new recognition task) to investigate the effects of acute physical exercise and active wakeful rest on salivary BDNF concentration, with samples collected from passive wakeful rest representing basal expression of BDNF.

1. Hypotheses

1.1 Study 1

H1: Moderate intensity physical exercise will lead to increased BDNF concentration compared to baseline.

H2: High-intensity exercise will lead to increased BDNF concentration compared to baseline.

H3: Increased BDNF concentration as a result of moderate intensity physical exercise will be less than that of high-intensity physical exercise.

H4: Low intensity physical exercise will have no effect on BDNF concentration.

1.2 Study 2

H1: Passive wakeful rest (control) will have no significant effect on BDNF concentration.

H2: Active wakeful rest will have no significant effect on BDNF concentration.

H3: Physical exercise will lead to increased BDNF concentration at timepoint 2 (post-intervention), compared to timepoint 1 (baseline).

H4: BDNF concentration, post-exercise, will be higher at timepoint 2 than at timepoint 3 (post-retention).

2. Method

2.1 Saliva collection and treatment

Participants were asked to remain seated and relaxed for 10 min prior to each saliva sample collection, with the exception of post-intervention sample collections which were obtained within a few min post-intervention. 10 min prior to each saliva sample collection, participants were asked to rinse their mouths with water and swallow in order to empty the mouth before each collection. During saliva sample collection, participants remained seated with their heads tilted slightly forward and passively dribbling into a pre-weighed tube while keeping orofacial movement to a minimum. Following the 2 min, the tube was weighed again to allow for estimation of saliva flow rate when the density of saliva was assumed to be 1.0 g.ml-1 as used in previous studies (Davison et al., 2009). When there was an insufficient amount of saliva at the end of 2 min, the process was repeated until an adequate amount was obtained.

After saliva collection, the samples were centrifuged for 5 min at 16,000 *g* to pellet gross debris with the supernatant stored at – 80 °C for later analysis. All saliva samples were thawed at room temperature only once prior to analysis. Samples were then centrifuged again for 5 min at 16,000 *g* to precipitate mucins and other debris and allow for the resulting clear supernatant to be analysed.

2.2 Salivary analysis

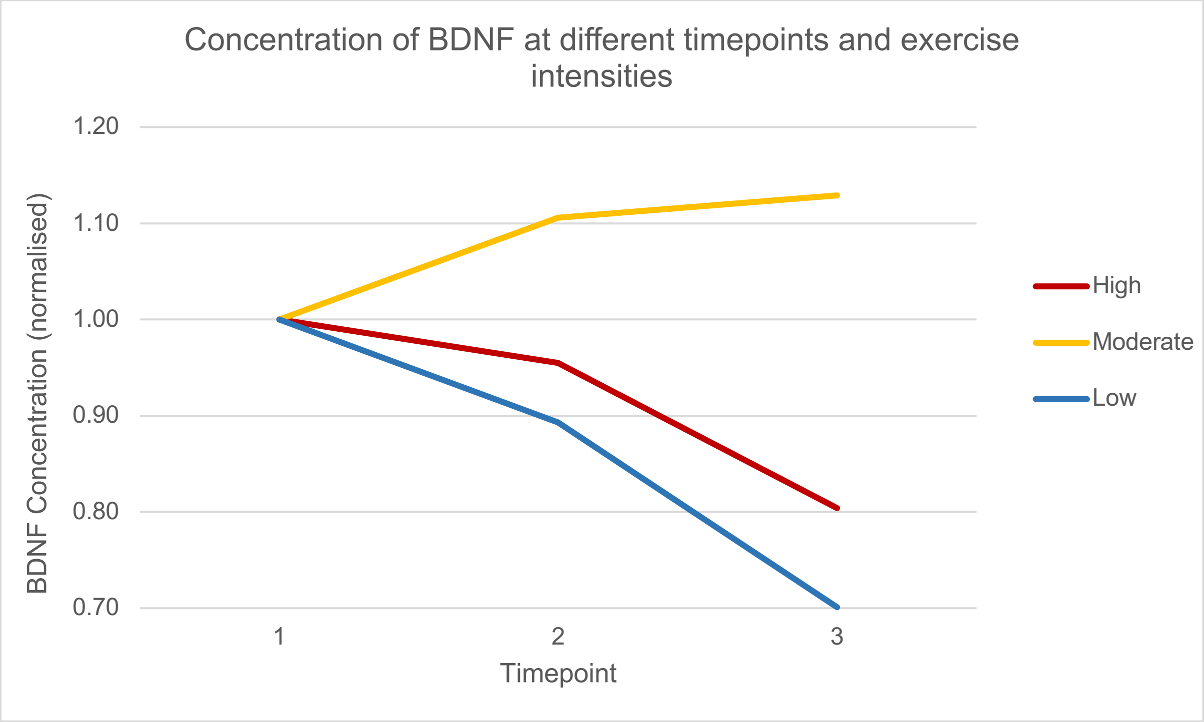
2.2.1 Blood contamination

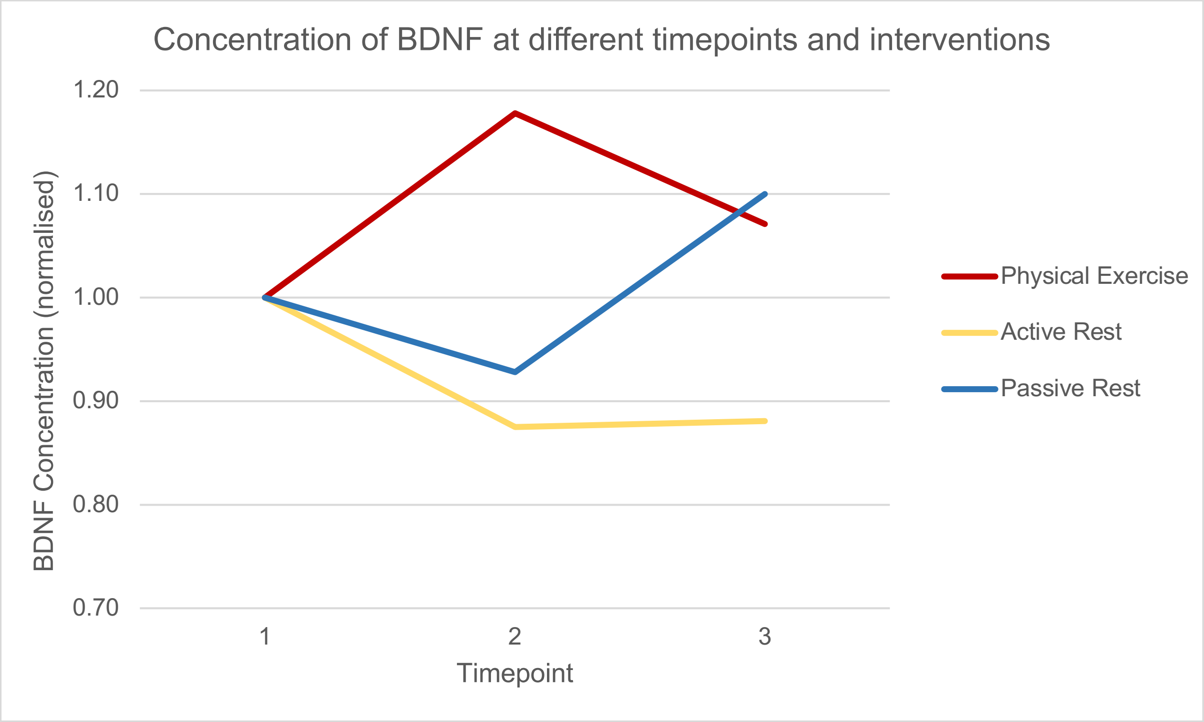
Aliquots of saliva were screened for blood contamination by the determination of salivary transferrin concentration using an enzyme-linked immunosorbent assay (ELISA) kit (Salivary blood contamination enzyme immunoassay kit, Salimetrics, State College, Pennsylvania, USA). If salivary transferrin concentration was greater than 1 mg.dL^{-1}, the sample was considered to be contaminated with blood and data for that sample was excluded. Based on 40 duplicated samples, intraassay coefficient of variation (CV) was 7.0%.

2.2.2 Salivary BDNF concentration

The concentration of salivary BDNF was determined using a commercially available high-sensitivity ELISA kit (EK0307 Human BDNF PicoKine™ ELISA Kit, Boster, Pleasanton, CA, USA). Based on 40 duplicated samples, intraassay CV was 6.5%.

3. Results





4. Discussion

Brain-derived neurotrophic factor (BDNF) is an important mediator of synaptic plasticity, as it, not only contributes to LTP, but is likely at the heart of plasticity-related processes underlying long-term memory (Coelho et al., 2013; Cunha et al., 2010; Heinonen et al., 2014).

Studies 1 and 2 were run in tandem with saliva sample collection at three timepoints (before intervention, after intervention, and after old/new recognition task) to investigate the effects of acute physical exercise and active wakeful rest on salivary BDNF concentration, with samples collected from passive wakeful rest representing basal expression of BDNF. However, due to the unforeseen circumstance of the freezer breaking down at the University of Kent Medway campus, all the saliva samples (alongside many other samples from other researchers) were rendered perished as the contents in saliva are unstable and susceptible to degradation at room temperature. Details of the hypotheses, methods, and preliminary results (from the few samples that were analysed before the freezer breakdown) are found in the appendix. Nevertheless, physical exercise has repeatedly demonstrated its capacity to facilitate the synthesis and release of BDNF (Heinonen et al., 2014; Hötting et al., 2016).

Earlier, I discussed how intensity may have affected the efficacy of the acute physical exercise intervention over 24h. Delving further into this train of thought, the notion that BDNF is a mediator of the effects of physical exercise on cognitive performance becomes more likely. For example, previous studies have demonstrated a linear dose-response relationship between physical exercise intensity and BDNF concentration (Chang et al., 2012; Knaepen et al., 2010). Additionally, previous studies have demonstrated greater memory performance for higher intensities compared to lower intensities when tested 24h post encoding (Hötting et al., 2016), as well as 7 days later (Roig et al., 2013) . This may, in part, account for the reduced performance scores after 24h following a bout of moderate-intensity physical exercise. Taken together, it can be argued that BDNF is a mediator of the effects of acute physical exercise on long-term memory, especially for periods of 24h or more.

Recently, Cocco, Podda, and Grassi (2018) reviewed studies linking tDCS to downstream molecular cascades that subsequently regulate BDNF. Here, the authors described the involvement of increased calcium (Ca^{2+}) level as a result of tDCS-induced membrane depolarisation (Cocco et al., 2018). This increased level of Ca^{2+} is linked to the possible initiation of the molecular pathways that lead to enhanced acetylation, which in turn modulates the transcription of BDNF (Cocco et al., 2018; Kornhauser et al., 2002). Therefore, it can be argued that the combined intervention led to increased BDNF release during the physical exercise and tDCS portions of the intervention. However, this would imply that the combined intervention would result in further enhancement in long-term memory performance compared to the physical exercise intervention due to the further increase in BDNF. Study 6 shows that this is not the case and indicates that other factors played a more prominent role at modulating memory performance.