THE BENEFIT OF AN ACUTE BOUT OF EXERCISE FOR PROCEDURAL CONSOLIDATION IS NOT RELATED TO AVOIDING A TEMPORARY REDUCTION IN MOTOR CORTICAL EXCITABILITY

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by
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ABSTRACT

Individuals in two separate experiments implicitly acquired a procedural skill which was tested after a 6-hr, wake-filled interval. In both experiments individuals that were exposed to a vowel counting activity immediately following procedural training exhibited successful procedural consolidation manifest as significant offline gain. This gain was eliminated by replacing the vowel counting task with a declarative learning task. The disruption in procedural consolidation demonstrated in both experiments confirms reports that declarative and procedural systems can interact during wakefulness. A novel finding revealed in Experiment 1, and replicated in Experiment 2, was that exposure to a brief bout of moderate intensity cardiovascular exercise immediately after procedural learning protected the newly acquired motor memory from interference introduced by declarative learning. These data suggest that the interplay between declarative and procedural systems can be modified by exercise. Experiment 2 examined the possibility that the exercise bout in Experiment 1 served to elevate cortical excitability at M1, eliminating the transient reduction that is displayed shortly after training in cases where procedural consolidation does not occur. Findings from Experiment 2 indicated that exercise does instigate an increase in M1 excitability during the immediate time period after practice. However, the increase in M1 excitability induced via exercise was not significantly greater than the increase that occurred for other learning conditions in the absence of exercise. Thus, the benefit of incorporating an acute bout of exercise for procedural learning is not dependent on the upregulation of excitability of a key neural site for procedural skill consolidation, M1.

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CHAPTER I

INTRODUCTION AND LITERATURE REIVEW

It has long been argued that the development of memories is dependent on unique systems that are designed to handle particular types of information. An early but common delineation proposed separate declarative and procedural systems responsible for the encoding of memory for fact and skill respectively (Cohen & Squire, 1980). Indeed, there are data implicating unique neural substrates for each of these memory systems (Squire, 2004). Brown and Robertson (2007) questioned whether these systems continue to operate independently once initial encoding is complete. They were specifically interested in determining if each memory system remained autonomous during consolidation of newly acquired memories, a process that occurs offline after the initial bout of training.

Stabilizing and enhancing memories through consolidation

Consolidation has been described as a process of strengthening memories (McGaugh, 2000; Diekelmann & Born, 2007) resulting in memory stabilization (Walker, 2005; Krakauer & Shadmehr, 2006; Korman et al., 2007) or enhancement (Walker & Stickgold, 2006). Stabilization is most commonly manifest as decreased susceptibility to interference. For example, memory for procedural skill is reduced when the initial training for this skill is followed by training of another procedural skill in close temporal proximity (Brashers-Krug et al., 1996; Walker et al., 2003). Increasing the time delay between the bouts of practice with each skill reduces the amount of interference. In the case of procedural consolidation, the primary motor cortex (M1) seems especially important as the application of slow frequency repetitive transcranial magnetic stimulation (rTMS) at this site, immediately after practice, also reduces memory for a procedural skill. In contrast, administration of rTMS after a greater time delay leads to an improvement in memory for the practice procedural skill that is similar to a control condition in which no stimulation was applied (Muellbacher, et al., 1998).

In certain cases, memories are not just stabilized but are enhanced. For example when practice of a procedural skill is followed by sleep rather than an equivalent period awake, performance of the skill actually improves beyond that observed at the conclusion of practice (Walker et al., 2003; Robertson, Pascual-Leone, & Press, 2004). This is despite a lack of any additional training. Data revealing both stabilization and enhancement have been interpreted as evidence that consolidation immediately following practice is critical for the ongoing development of a novel, initially labile memories. Despite the generally wide acceptance of the critical role played by consolidation for determining the fate of a newly acquired memory, Breton and Robertson (2014) noted that little is known about how this memory process is regulated and controlled.

Declarative and procedural memory systems can be used flexibly to support procedural consolidation

Given the prevailing assumption that declarative and procedural systems are distinct, it is not surprising that the studies that used a behavioral interference paradigm to examine the role of post-practice consolidation focused exclusively on either the declarative or procedural system. That is, when addressing offline processing of a procedural memory, the interference used to disrupt consolidation involved using a task that relied on the same memory system (i.e., a procedural skill) (Walker et al., 2003; Rhee, Reichman, & Wright, 2016). A novel question posed by Brown and Robertson (2007) asked if procedural consolidation could be disturbed by inducing interference from learning within the declarative system immediately after practice of a procedural skill. This question was predicated on the possibility that, at least for consolidation, declarative and procedural systems interact rather than function in isolation.

To address this issue, Brown and Robertson had participants implicitly acquire a 12-element serial reaction-time task (SRTT)[1] that was immediately followed by declarative learning consisting of repeated list recall or a vowel counting task that demanded relatively less learning. The extent of procedural consolidation was evaluated 12-hrs after practice was concluded. When practice of this procedural skill was followed by the vowel-counting task, performance of the SRTT was superior to that observed at the end of training 12-hrs earlier. Procedural skill enhancement was observed. This was congruent with previous work that revealed offline gain for implicit motor sequence learning across a wake-filled interval (Robertson, Pascual-Leone, & Press, 2004). Alternatively, the inclusion of a bout of declarative learning immediately after SRTT practice, impeded procedural consolidation assessed after the 12-hr wake filled interval. Moreover, the extent of interference observed was correlated with performance of the declarative learning task. That is, greater success at recalling the items from the word lists, led to smaller offline benefits for the procedural skill after the 12-hr interval supporting the claim that declarative and procedural systems interact (see also Brown & Robertson, 2011).

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[1] All participants that exhibited explicit knowledge of more than 3-elements of the 12-element sequence during the 12-delayed recall test were removed from all analyses to focus exclusively on consolidation of an SRTT acquired implicitly.

Despite declarative learning obstructing procedural consolidation across a wake-filled interval, following sleep, the procedural skill exhibited the anticipated benefit from consolidation.[2] Taken together, these findings support the claim that the declarative and procedural memory systems are less encapsulated than once assumed (Cohen & Squire, 1980). Instead these systems have a reciprocal relationship while also exhibiting some flexibility that results in them sometimes operating in concert (i.e., declarative learning interfering with procedural consolidation over a wake-filled interval) while at other times functioning separately (i.e., declarative learning failing to inhibit procedural consolidation over a sleep-filled interval).

Changes in functional connectivity to account for flexible use of declarative and procedural memory systems for procedural consolidation

Brown and Robertson (2007) contemplated a number of biologically plausible models that might account for the finding that declarative and procedural systems interact over a wake period (i.e., procedural consolidation is disrupted when the declarative system is engaged) but were effectively independent during sleep (i.e., procedural consolidation is successful despite being followed immediately by declarative learning during practice). Figure 1 a-d (taken from Brown & Robertson, 2007, Figure 8, p. 10474) provides an overview of these alternatives. In the first case (Figure 1 a and c), distinct neural circuits support the development of declarative and procedural memory. As noted earlier, there are data supporting the claim M1 plays a crucial role for procedural consolidation (Muellbacher, et al., 1998) as well as distinct segments of the striatum

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[2] In a second experiment, Brown & Robertson (2007) also revealed that practice with a procedural skill (i.e., SRTT) hindered consolidation of prior declarative learning offering further support for the interplay between the declarative and procedural memory systems. The present work however is focused on procedural consolidation hence the emphasis on the experiment involving this process (i.e., Brown & Robertson, 2007, Experiment 1).

(Albouy, et al., 2008; Dayan & Cohen, 2010). In contrast, neural circuitry involving the medial temporal lobe including the hippocampus, the inferior parietal cortex (IPL) (Robertson, 2009), and the neocortex may be particularly important for declarative consolidation (Robertson et al., 2005; Peigneux et al., 2006; Takashima et al., 2006; Rasch et al., 2007; Robertson, 2009). Despite the unique neural architecture for declarative and procedural systems, Brown and Robertson (2007) propose that interactions between these systems might arise as a result of processes performed within these circuits being coordinated by an alternative neural structure, such as DLPFC, that acts as an executive (see Figure 1a).

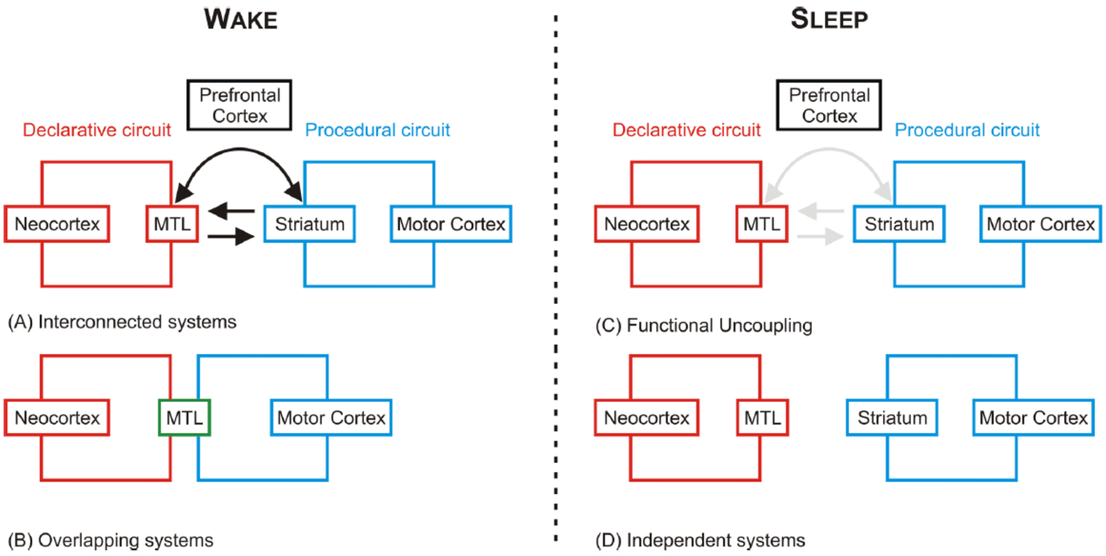

Figure 1. Biological architecture supporting declarative (red) and procedural (blue) systems during wake (left panel) and sleep (right panel). Processes being executed within the declarative and procedural systems may be supervised by executive sites (A) or share a common neural substrate (B). Either account is consistent with interference of procedural consolidation via declarative learning during wake reported by Brown and Robertson (2007). Successful procedural consolidation that occurs during sleep, despite declarative learning occurring after procedural skill acquisition, can be explained by either a disengagement of the executive sites (C) or the emergence of separate pathways (D). Thus, sleep promotes functional connectivity distinct from that present during a wake period that has unique consequences for the implementation of procedural consolidation.

A slightly different account views the declarative and procedural systems sharing some critical neural resource. Again, this is not unreasonable given recent theorizing about the role of the MTL or more specifically the hippocampus for consolidation during both declarative and procedural learning (Albouy et al., 2008; Albouy et al., 2013). Thus, the interference reported during a wake period by Brown and Robertson may have emerged as a result of competition for the same neural resource (e.g., MTL in Figure 1b). This competition is eliminated when separate pathways become available as a result of decoupling the circuits that support procedural and declarative consolidation during sleep. Thus, procedural consolidation occurs unimpeded.

Robertson (2012) envisions wake and sleep periods as being characterized by distinct functional connectivity that create "brain states" that have unique consequences for promoting changes in the organization of human memories (i.e., support consolidation). Connectivity is such during the wake period that the declarative and procedural systems interact (see Figure 1a and b, also Robertson 2009) and thus lead to interference. By contrast, simultaneous consolidation of different memories within these systems can be undertaken when systems disengage. The latter occurs in an alternative state of functional connectivity that emerges during sleep. More detailed discussion of the advantages and shortcomings of such flexible interaction between declarative and procedural system is beyond the scope of the present work. However, this issue has been elaborated by Robertson (2009). More importantly for the present work is the suggestion that unique brain states, and concomitant implications for consolidation, may emerge as a result of other factors such as age or developmental stage (Robertson, 2012), practice extent (Robertson, 2009), and/or incentive (Abe et al., 2012; Breton & Robertson, 2014). In the present studies, an acute bout of exercise is considered as a novel intervention during learning that might also be a candidate to induce a neural environment conducive to procedural consolidation.

Acute exercise and procedural consolidation

Exercise has been identified as an important for learning and memory (Robertson & Takacs, 2017). In the case of procedural learning, a robust long-term benefit has been revealed following just a single session (Roig, et al., 2012). Advantages from acute exercise appear broad-based having being reported to facilitate the performance of visuo-motor tracking (Roig, et al., 2012) and motor sequence tasks (Ostadan et al., 2016; Rhee et al., 2016). The most frequent form of exercise associated with procedural skill improvement is cardiovascular exercise that is tailored to the participant's fitness level. In this regard, both moderate (Rhee et al., 2016) and high intensity cardiovascular exercise (Roig, et al., 2012) have been used to aid procedural skill retention.

Current thinking is that exercise exerts its influence by modulating procedural consolidation that occurs after a bout of practice (Roig, et al., 2012; Rhee, et al., 2016; Jo et al., 2018). For example, Rhee et al. (2016) inserted 20-min of moderate intensity cardiovascular exercise between practice of a target motor sequence and additional practice with a second novel motor sequence 2-hours later. The primary objective of this work was to explore the possibility that exercise expedites post-practice consolidation that fosters more rapid stabilization of the labile memory for a novel motor task thus rendering it less susceptible to interference from subsequent practice of another motor task. As predicted, despite exposure to interfering practice, a small offline improvement at test, rather than significant forgetting, was observed for the individuals that exercised compared to those individuals that did not exercise (see also Lauber, Franke, Taube, & Gollhofer, 2017).

Unfortunately, Rhee et al. (2016) and others (e.g., Roig et al., 2012) administered retention tests after their participants experienced a night a sleep. Sleep has a well-documented influence on post-practice consolidation (Walker et al., 2003). Since all conditions in Rhee et al. were exposed to sleep, this factor alone cannot account for exercise-mediated benefits of exercise. However, these data cannot rule out the possibility that exercise operated in conjunction with sleep to induce improved procedural consolidation (see Brown & Robertson, 2007). To eliminate this possibility, Jo et al. (2018) revisited this issue but used a retention interval that should be sufficient for consolidation to occur (i.e., 6-hr) but was wake not sleep-filled. Despite the removal of sleep, Jo et al. reported that exercise provides some protection from interference, independent of sleep, presumably by enhancing procedural consolidation. Moreover, Jo et al. proposed that the inclusion of exercise during the learning process modifies functional connectivity (i.e., brain state) within critical neural circuits supporting procedural consolidation from that that exists in the absence of exercise in a manner similar to that described by Brown and Robertson during a period of sleep. [3]

This latter proposal is somewhat tentative and based on data gathered using a paradigm and tasks that were quite distinct from that used by Brown and Robertson (2007). To address this shortcoming, Experiment 1 was designed to directly assess the viability of this account by examining the influence of an acute bout of exercise on procedural consolidation in the case where it is disrupted by declarative learning. The novel prediction from Experiment 1 was the inclusion of an exercise would mitigate the interfering qualities of declarative learning for procedural consolidation allowing offline gains to be observed. Experiment 2 was planned to address the claim that the benefit of exercise anticipated in Experiment 1 for procedural consolidation is a result of modifying the neural environment from that present for the learner in the situation in which exercise is absent. Single-pulse transcranial magnetic stimulation (TMS) was used to evaluate if exercise-mediated offline gain is associated with maintenance of M1 excitability

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[3] This proposal doesn't necessarily mean that exercise de-couples the same neural sites that might be shared by the declarative and procedural memory systems (e.g., role of MTL or DLPFC) as in sleep. Rather that, like sleep, exercise reduces in, as yet, some unspecified way the interdependence on certain neural sites by the two memory systems.

immediately after practice which has been proposed to be a post-training physiological marker of ongoing consolidation (See Tunovic et al., 2010; Breton & Robertson, 2014; Ostadan et al., 2016; Robertson & Takacs, 2017).

CHAPTER II

EXPERIMENT 1

As was the case in Brown and Robertson (2007) individuals learned a 12-element SRTT which was followed by either a bout of declarative learning or a vowel counting task 1-hr later. An additional experimental condition was included that involved the insertion of a 20-min bout of moderate intensity cardiovascular exercise performed on a bicycle ergometer. The extent of procedural consolidation was inferred from the change in performance at the conclusion of training and the test administered after a wake-filled 6-hr interval.

It was expected that while an offline gain for the SRTT would occur for individuals that experienced vowel counting as interference; this gain would be lost when vowel counting was replaced by declarative learning. The reduction in offline gain for the procedural skill is expected to be correlated to the degree of declarative learning suggestion of an interaction between declarative and procedural systems. Adding an acute bout of exercise after SRTT practice but prior to declarative learning, was predicted to lead to the recovery of the offline gain from procedural consolidation across a wake interval.

Methods

Participants

A total of 57 undergraduate right handed students were recruited as participants for Experiment 1. Thirty-seven participants were included in all of the following reported analyses as a result of meeting the declarative knowledge requirement of the SRTT (i.e., < 4 elements correct in a post-experiment verbal recall test). Twenty participants (35% of total participants) were thus excluded from Experiment 1. The individuals assigned to each of the three experimental conditions in Experiment 1 did not differ as a function of age [$F(2,34) = 0.57$, $p=0.57$], body mass index [$F(2,34) = 0.77$, $p= 0.47$]; resting heart rate [$F(2, 34) = 0.20$, $p=0.82$], heart-rate predicted maximum, [$F(2,34) = 0.57$, $p=0.57$], and heart rate reserve [$F(2,34) = 0.19$, $p=0.83$]. These data are reported in Table 1.

Table 1. Demographic (mean, SD) of all participants in Experiment 1

	N	Male	Female	Age (Yrs)	BMI	Resting Heart Rate (RHR)	HR age-predicted max (HRmax)	Heart Rate Reserve (HRR)	Declarative knowledge of SRTT
VC	12	1	11	19.25±1.14	21.21±2.08	73.42±5.14	194.53±0.80	121.11±5.58	2.33±1.15
WL	12	3	9	19.42±1.08	22.40±2.76	71.25±11.96	194.41±0.76	123.16±8.01	2.50±1.73
WL+EXE	13	2	11	19.85±1.91	21.60±2.27	72.46±7.01	194.11±1.34	121.65±6.75	2.23±1.42
Total	37	6	31	19.51±1.43	21.73±2.37	72.38±8.30	194.34±1.00	121.96±8.34	2.35±1.42

Tasks

Procedural Learning: Serial Reaction Time Task (SRTT). A SRTT previously adopted to encourage implicit procedural learning was used (Brown & Robertson, 2007b). Specifically, a solid circular visual cue appeared at any one of four possible positions organized horizontally in the lower third of a computer screen. The left most visual cue was labelled “1” whereas the rightmost, “4.” Each of the four horizontal positions corresponded to one of the four spatially compatible keys on a computer keypad on which the fingers of their right hand rested. When a target was illuminated, participants were instructed to press the corresponding key on the keyboard as accurately and quickly as possible. The visual target remained illuminated until the correct key was pressed at which time the next visual signal in a predetermined order for a repeating 12-element sequence was illuminated. The visual signals for the SRTT presented on the PC monitor followed the order, 2-3-1-4-3-2-4-1-3-4-2-1, (Brown & Robertson, 2007a).

Declarative Learning: Word List (WL). A word list previously used and described as involving declarative learning was used in Experiment 1 (see Brown & Robertson, 2007b). For this task, a word, selected from a predetermined set of 16 words drawn from the California Verbal Learning Test, was presented on a computer monitor for 2 s. After the 2-s presentation of the initial word, a new word from the set was then presented and this presentation scheme continued until all 16 words in the list had been viewed by the participant. Once all 16 words have been viewed, participants will be asked to recall, in any order, as many of the words from where just presented in the previous list. When this recall test was completed, the same 16 words were presented to the participant an additional four times, a total of five presentations, with the words being presented in the same order each time and recall being requested following viewing of the complete set of 16 words. Ten minutes after the fifth recall test, each individual was asked to complete an additional free recall of the word list.

Declarative Task: Vowel Counting. As revealed in previous work, individuals can perform a declarative task that does not entail learning. Such a task, vowel counting, was used in Experiments 1. Participants were shown a list of 16 nonsense letter strings, varying in length from three to 12 letters. Participants were required to count and then state the number of different vowels within a string. Each string was presented on the computer monitor for 2 s and, like the WL, involved a new letter string being presented until 16 nonsense letter strings had been viewed. Consistent with the protocol for the WL, each participant was exposed to five presentations of the list of 16 nonsense letter strings, completed the counting task, and articulated the vowel count after each trial. After the presentation of the fifth set was complete, a 10 min interval was allowed before the 16 nonsense letter strings were again presented followed by an assessment of the number of different vowels within each string. Any single nonsense letter strings was not repeated.

Acute Bout of Exercise. Some participants performed an acute bout of aerobic exercise between the practice of the SRTT and the WL task. Prior to participation in Experiment 1, resting heart rate (RHR) was obtained from all participants using a Polar heart rate (HR) monitor (E600). To control for different fitness levels, the intensity of the acute exercise bout was individually tailored using each individual's heart rate reserve (HRR) calculated as:

$$\text{HRR} = (\text{HR}_{\text{age-predicted max}} - \text{RHR})$$

Where,

$$\text{HR}_{\text{age-predicted max}} = 208 - (0.7 \text{ x age})$$

(Tanaka, Monahan, & Seals, 2001)

Participants assigned to the exercise condition began with a 3-min warm-up at 60% HRR (HRR * 0.6 + RHR) on a bicycle ergometer. This was followed by 20-mins of exercise at 80% HRR (HRR * 0.8 + RHR). During the entire acute exercise bout, participants were required to maintain a cadence of 75 rpm. After the completion of an acute exercise bout, all individuals cycled at 0 W for an additional 3-min during a cool-down period.

Procedure

The timeline for all key features of Experiment 1 are provided in Figure 2. All individuals were first exposed to training with the SRTT. Performance of the SRTT began with a short training block that involved 15 repetitions of the 12-element sequence (i.e., 180 trials), followed by a longer period of practice that was made up of twenty-five repetitions or 300 total trials. Test block 1 followed practice and included 15 repetitions of the repeated sequence (i.e., 180 trials). Fifty random trials always preceded and followed a practice or test block with the repeating SRTT.

One hour later individuals was assigned to conditions that incorporated either a delarative learning activity that involved a word list (WL condition) recall task or another verbal task that involved vowel counting (VC condition). These activities were executed as described in the relevant task section of the methods. A separate set of individuals were assigned to the WL+EXE condition also performed the WL 1-hr after practice of the SRTT but were also exposed to an acute bout of exercise immediately after procedural skill training was complete but prior to declarative learning.

Individuals in all experimental conditions (WL, VC, WL+EXE) completed Test Block 2 6-hr after practice of the SRTT that again consisted of a single block with 15 repetitions (180 trials) of the repeated sequence. As was the case with Test Block 1, 50 random trials preceded and followed the trials with the repeating SRTT. It was important that performance of the SRTT was implicit. For this reason, an assessment of each individuals' explicit knowledge of SRTT was made after Test Block 2. The individuals that reported knowledge of greater than four elements of a practiced SRTT during a verbal recall test were removed from all analyses.

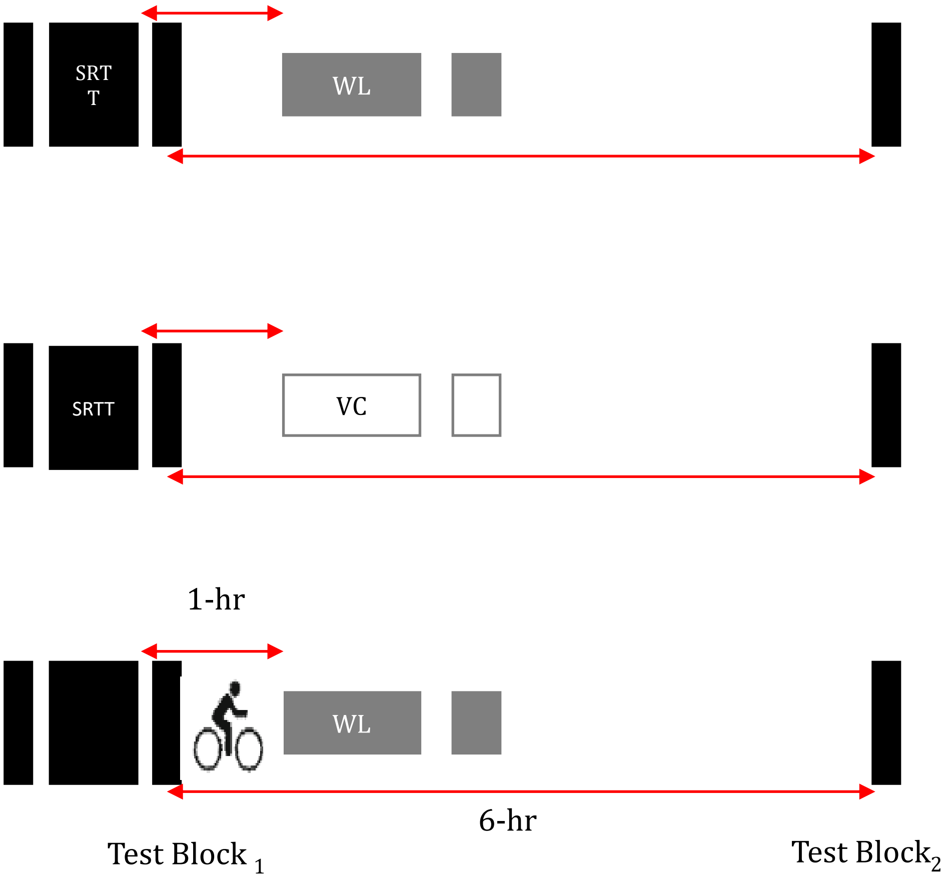

Figure 2. Three experimental conditions were included in Experiment 1: WL, VC, and WL+EXE conditions. All participants first practiced the SRTT (procedural skill) and Skill was determined at the conclusion of this bout of practice during Test Block 1. Individuals in the WL condition then performed a word list recall task (declarative learning) which was subsequently tested 10-min after the conclusion of this bout of practice. A different set of individuals performed a vocal counting activity after practice of the SRTT (VC condition). This condition serves as a control. VC has been argued to engage the declarative system but does not involve learning. Finally, another set of participants followed the same protocol as the WL condition with the addition of a bout of exercise immediately after practice with the SRTT (WL+EXE condition). All participants completed Test Block 2 with the SRTT six hours after the initial training was completed.

Analyses

Response time was defined as the time from the imperative stimulus and pressing the appropriate key associated with the visual signal presented. A learning score was determined by subtracting the average response time of the final 50 sequential trials from the average response time of the 50 random trials that followed (Brown & Robertson, 2007a). A learning score was calculated for Test Block 1 to determine skill at the conclusion of practice. A subsequent learning score was used to calculate skill for Test Block 2 after the 6-hr interval. The difference between skill at Test Blocks 1 and 2 reflected the extent of procedural consolidation over the 6-hr wake period. The extent of procedural consolidation for each experimental conditions (WL, VC, WL+EXE) was assessed using a mixed-model analysis of variance (ANOVA). Any differences were assessed using simple main effect analyses and post-hoc tests.

Results

Procedural Consolidation and Type of Interference

A 3 (Condition: WL, VC, WL+EXE) x 2 (Test Block: 1, 2) ANOVA with repeated measures on the last factor for skill revealed a significant main effect of Test Block, F (1, 34) = 16.96, p<.01 as well as a significant condition x test block interaction, F (2, 34) = 7.16, p<.01. Simple main effect assessment of this interaction indicated that there was no significant difference for skill as a function of condition [F (2, 34) =0.96; p=0.40, VC: M = 39ms, SEM =13ms; WL: M = 53ms SEM = 10ms; WL+EXE: M = 33ms, SEM = 9ms, see Figure 3b] at Test Block 1. However, condition, that is the nature of the interference or the presence of exercise following practice of the SRTT, had a significant impact on skill after the 6-hr wake filled interval, F(2,34) =4.06, p<.01. Post-hoc analysis indicated that skill for the VC (M = 71ms, SEM = 6ms) did not differ from WL+ EXE condition (M = 70ms, SEM = 8ms). However both of these conditions exhibited greater skill than that observed for the WL condition at Test Block 2 (M = 46ms, SEM = 6ms). Individuals in both the VC [t (11) = 3.08, p<.01, M = 31ms, SEM = 10ms] and the WL+EXE [t (12) = 4.73, p<.01, M= 37ms, SEM = 8ms) benefitted from procedural consolidation, manifest as a significant increase in skill across the 6-hr wake-filled interval. This was not the case for the individuals in the WL condition who displayed no significant change in skill from the end of training to the test administered 6-hr later [t (11) = 0.79, p = 0.45, M= -7ms, SEM = 8ms) (see Figure 4).

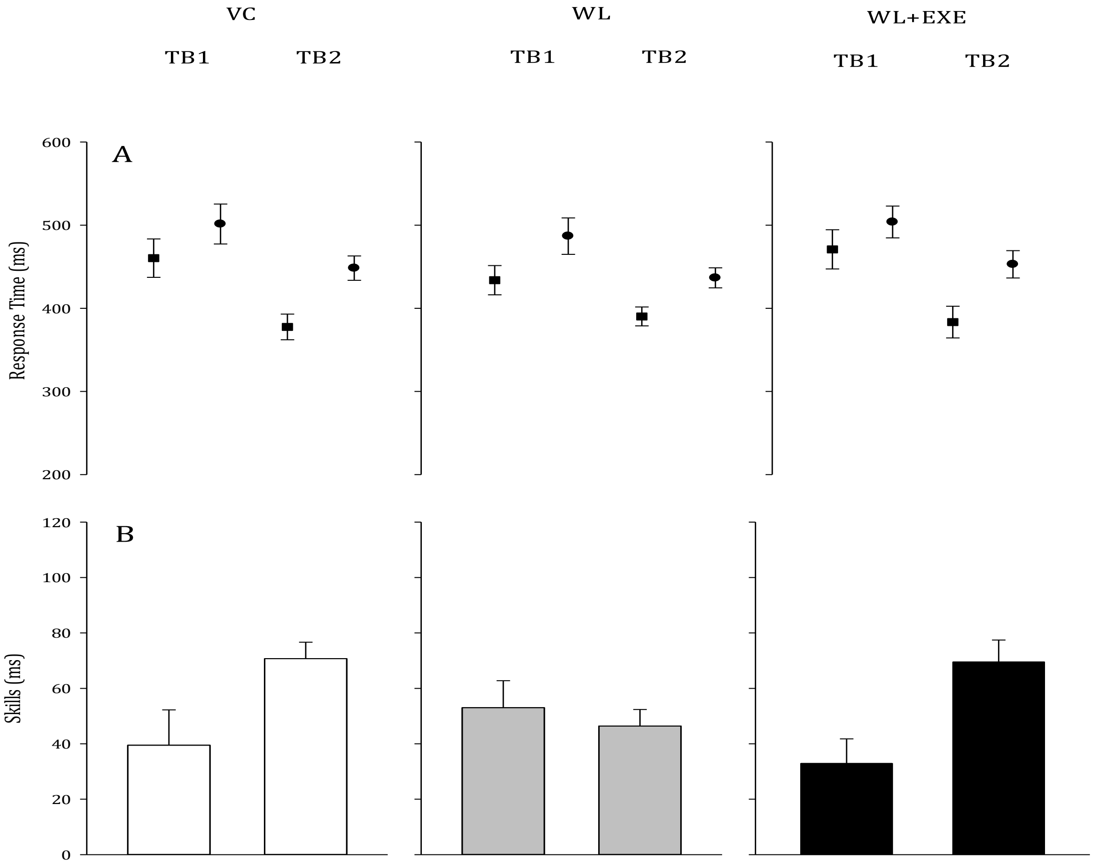

Figure 3. Mean response time (panel A) was calculated for the last 50 sequence trials (square symbol) and the 50 random trials (circle symbol) that occurred at the conclusion of practice of the SRTT (Test Block 1, TB1) and during Test Block 2 (TB2) for each of the three experimental conditions (VC, WL, WL+EXE). Skill was determined as the difference between mean response time for the sequence and random trials at TB1 and again for TB2 after 6-hr (Panel B).

An independent t-test on WL recall for the WL and WL+EXE conditions failed to reveal a significant effect, t(23) = 0.12, p=0.91. Thus, declarative learning was similar in both the WL (M = 15.2 items, SEM = 0.52 items) and WL+EXE (M = 15.1 items, SEM = 0.54 items) conditions and in both cases. Overall WL recall was extremely high.

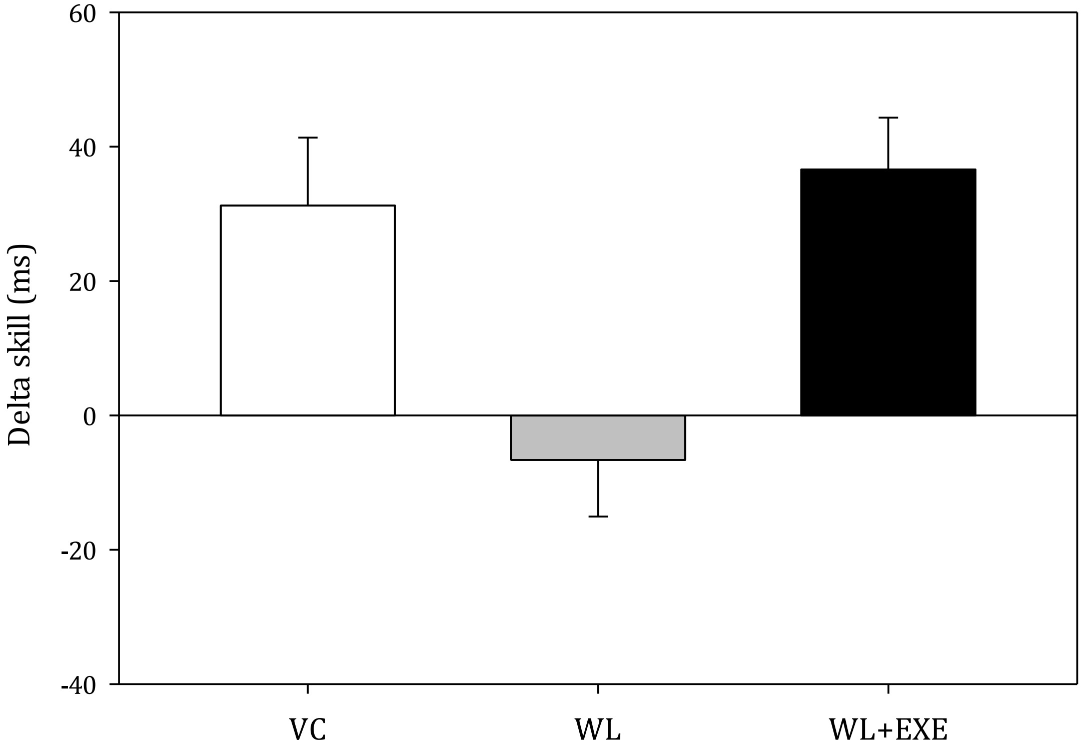

Figure 4. Mean skill was calculated at TB2 and TB1. The difference in skill (Δ skill) between these two time points reflects procedural consolidation and is present in this figure for the VC, WL, WL+EXE conditions. A larger score in this figure reflects greater procedural consolidation. In Experiment 1 both VC and WL+EXE support procedural consolidation which was not the case for the WL group.

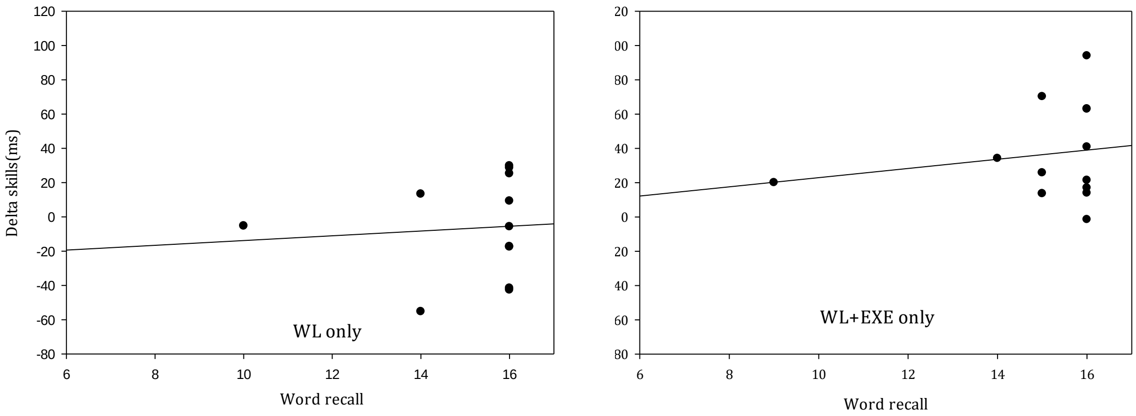

Figure 5. The relationship between the change in skill at TB2 and TB1, that is, Δ skill which reflects procedural consolidation, and performance on the WL recall test for the individuals in the WL condition only. This relationship was not significant (left panel). The relationship between the change in skill at TB2 and TB1, that is Δ skill which reflects procedural consolidation, and performance on the WL recall test for the individuals in the WL+EXE condition only. This relationship was not significant (right panel).

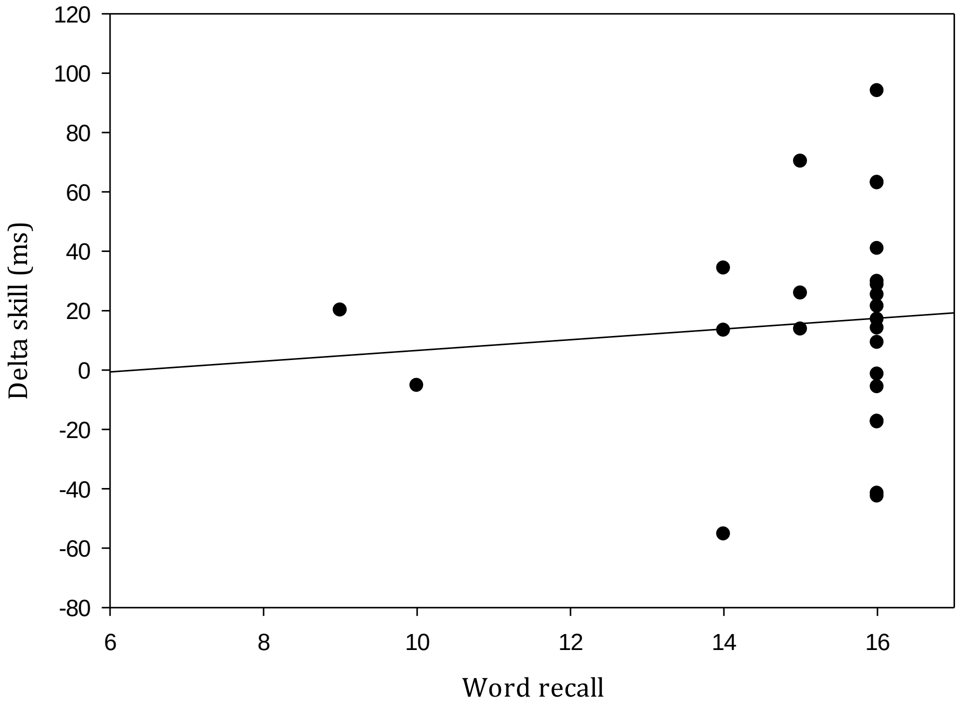

Figure 6. The relationship between the change in skill at TB2 and TB1, that is, Δ skill which reflects procedural consolidation, and performance on the WL recall test for all of the individuals in the WL and WL+EXE conditions. This relationship was not significant.

Correlation: Procedural consolidation and declarative learning

According to Brown and Robertson (2007) and a basic premise of any account that proposes some interaction between declarative and procedural systems is that the extent of declarative learning following procedural learning should mediate the amount of procedural consolidation. To evaluate this prediction, the WL recall for each individual in the WL and WL+EXE conditions was correlated with Δ skill (i.e., offline gain) exhibited between TB2 and TB1. When this assessment was conducted for data from the WL condition only, there was no significant correlation (r^2=0.007, *F*=0.08, *p*=0.79, Figure 5, left panel). The same analyses performed on the data from the WL+EXE condition only was also not significant, (r^2=0.04, *F*=0.39; p=0.54, see Figure 5, right panel). Combining these data (WL and WL+EXE) still failed to reveal a significant effect, (r^2=0.01, *F*=0.20; p=0.66 see Figure 6). The lack of correlation in these assessments may have resulted from the large numbers of individuals in both conditions exhibiting a very high level of recall of the WL. Specifically, 92% of the individuals from the WL and WL+EXE conditions scored at least 15 of a possible 16 items correctly. Thus, general performance on this task (i.e., declarative learning) appears to be superior in Experiment 1 than reported in Brown & Robertson (2007).

Recall, that the intent in this work was that procedural learning unfolded in an implicit manner. Indeed, individuals that recalled greater than 4-elements of the SRTT correctly in a post-experiment verbal recall test were deemed to have explicit knowledge of the motor skill and were thus removed from the reported analyses (see Brown & Robertson, 2007). As a result of this criterion, 35% of the participants that completed Experiment 1 were eliminated. This was similar to that reported by Brown and Robertson (2007) who removed 26% of their subjects. For the participants that were included in subsequent analyses, a 3(Condition: VC, WL, WL+EXE) one-way between-subject ANOVA was conducted on the degree of declarative knowledge of the SRTT. As expected, based on the exclusivity criteria, this analysis failed to reveal a significant main effect of Condition, F (2, 34) = 0.11, p=0.90. As indicated by this analysis, declarative knowledge for the SRTT at the conclusion of Experiment 1 was similar for the WL (M = 2.5 elements, SEM = 0.3 elements), VC (M = 2.3 elements, SEM = 0.3 elements), and the WL +EXE (M = 2.2 elements, SEM = 0.4 elements) conditions. Furthermore, there was no correlation between participants' declarative knowledge for the WL and declarative knowledge of the SRTT for the individuals in the WL (r^2=0.01; F = 0.74; p=0.41) or WL+EXE (r^2=0.04; F =2.51; p=0.14) conditions. This suggest that any influence of declarative learning from learning the WL was not influencing the accumulation of declarative knowledge of the SRTT.

Discussion

Procedural consolidation occurs across a wake-filled period

Consolidation has long been considered critical for memory within the declarative system (McGaugh, 2000). Procedural consolidation has been demonstrated for both explicit and implicitly acquired motor skill (Walker et al., 2003; Robertson, et al., 2004). Explicit motor skills most often require a period of sleep to show offline gains as a result of consolidation. In contrast, for implicitly acquired motor skills, consolidation affords offline performance improvement across a wake period (Robertson et al., 2004; Brown & Robertson, 2007a, 2007b).

The present experiment focused on memory for an implicitly learned 12-element motor sequence. Implicitly learning this motor skill was defined in the present context as an individual recalling less than four elements of the motor sequence during a verbal recall test at the conclusion of the experiment. Despite not informing participants of the repeating nature of the motor sequence in Experiment 1, approximately 35% of the subjects could verbally articulate a significant part of the sequence. Performance of these individuals was not the focus of the present experiments. The remaining individuals learned the motor skill with limited or no conscious knowledge of the motor sequence. Some of these individuals despite performing a vowel counting activity immediately after practice of the SRTT, exhibited considerable offline gain amounting to a 79% increase in skill from the end of practice until the delayed test. These data then are consistent with previous data, in which no interfering activity occurs after SRTT practice, demonstrating that procedural consolidation can occur across a wake-filled interval (see Robertson et al., 2004).

Declarative and procedural systems can be linked

Data from Experiment 1 also confirmed earlier findings of Brown and Robertson (2007a, b) that procedural consolidation that occurs over a wake-filled interval can be impeded by engaging in a WL recall task immediately after practice of the procedural skill. In the present study, learning the word list after practicing the motor sequence completely eliminated any offline gain but did afford stabilization. That is, the level of skill observed at the end of practice was still present during the test 6-hrs later. Given the vowel counting task involved similar perceptual process to the word learning task it appears declarative "learning" must be involved in order to disrupt procedural consolidation.

These data are important because they verify the claim made by Robertson and colleagues that the declarative and procedural learning systems are not entirely encapsulated systems, at least for the purpose of consolidation, serving only knowledge or memories assumed to reside in one of the systems. Rather, in certain circumstances, the systems interact either by being governed by a common executor (e.g., DLPFC) or from sharing a neural resource to support consolidation (e.g., MTL, Albouy et al., 2013). When this occurs, procedural consolidation suffers.

Brown and Robertson as well as others (Breton & Robertson, 2014, 2017) argue that this type of interaction doesn't happen all of the time when consolidating procedural skills. Indeed, Brown and Robertson (2007) demonstrated that despite being exposed to declarative learning soon after practice with an SRTT, if the learner then experiences an interval that is sleep-filled, procedural consolidation is implemented unobstructed. Robertson and colleagues argued that during wake and sleep quite different brain states are instantiated, likely this refers to distinct patterns of functional connectivity. When procedural consolidation occurs unfettered, this account proposes that any link (i.e., functional connectivity) between the declarative and procedural systems has been uncoupled.

It should be noted that an important finding reported by Brown and Robertson 2007a, b) was the relationship between the level of word recall and the degree of procedural consolidation. That is, the greater the knowledge of the word list, the greater the reduction in offline gain because the shared features of the declarative system being placed under load during wake. In Experiment 1, we did not observe this relationship. However, the nature of the present data, that is word recall was extremely high, may have masked any relationships that might exist.

Acute exercise facilitates post-practice consolidation in the absence of sleep

The novel finding from Experiment 1 centers on the WL+EXE condition. For this condition, despite having a WL recall activity after SRTT training was complete, individuals still exhibited significant procedural consolidation after 6-hr. Thus, the acute bout of exercise was sufficient to protect the procedural memory that was formed during training such that it could undergo subsequent consolidation.

This finding is congruent with a number of other studies that have recently argued that an acute bout of exercise can influence post-practice consolidation processes (Roig et al., 2012; Rhee et al., 2016; Jo et al., 2018). Importantly, this is the first demonstration that exercise inserted in the post-practice interval, independent of sleep, can provide offline enhancement. Most previous studies have administered test phases that included a night of sleep (Roig, et al., 2012; Rhee et al., 2016) or provided the exercise prior to training (Lauber et al., 2017). Jo et al. did utilize a sleep-free interval and reported an increase in performance at test for an exercise condition. However, this improvement was not significantly better than that observed for a no-exercise control.

One interpretation of the reported exercise-mediated consolidation, based on the model of Brown and Robertson (2007), is that exercise creates a unique "brain state" that is different from that present for the learner when both procedural and declarative learning occur close in time and in the absence of exercise. Sleep is an alternative factor that has been proposed to induce a neural environment suitable for the implementation of consolidation. Indeed, Breton and Robertson (2014, 2017) implied that there may be other common experiences that support consolidation including incentive, developmental stage and even exercise.

The notion that exercise might change the state of entire circuits central to procedural consolidation or at a minimum some individual components of these circuits, is not new. M1 has been identified as central to consolidation of motor skill (Muelbacher, et al., 1998) (also see Figure 1). For example, applying 1 Hz repetitive TMS at M1 has been shown to eliminate contribution to motor memory from post-practice consolidation. Administering the same form of stimulation after a much longer time delay or at an alternative neural site demonstrated both the temporal and spatial specificity of this effect. Ostadan et al. (2016) recently reported that exposure to a brief bout of exercise after practice of a procedural skill increased cortical excitability at M1 beyond that observed for a no-exercise condition. More importantly, the increase in exercise was moderately associated with subsequent offline gain for the practiced skill. These data then suggest that exercise can influence the existing state of a key neural player and that changing the state of M1 via exercise can influence the resultant offline change in performance.

CHAPTER III

EXPERIMENT 2

An additional finding regarding the level of cortical excitability at M1, reported by Tunovic, Press, and Robertson (2014), may be important for probing how exercise facilitates procedural consolidation. Tunovic et al. noted that cortical excitability at M1 does not change dramatically immediately after learning a motor skill for situation in which offline enhancement occurs. However, a temporary decrease in cortical excitability at M1, up to 30%, has been observed in cases where motor skills fail to show any gain. Recently, Tunovic et al. manipulated cortical excitability using non-invasive stimulation to demonstrate that the status of cortical excitability at the conclusion of practice can determine the fate of the motor skill memory. For example, applying theta burst stimulation using TMS to induce a decrease in M1 excitability was shown to prevent offline gain. Alternatively, eliminating the decline in excitability using an alternative theta-burst protocol, ensured offline improvements. Taken together these data led Breton and Robertson (2014) to claim that a significant decrease in cortical excitability may be a physiological signal that acts as a brake to prevent subsequent memory consolidation during wakefulness.

Returning to the present work, it is possible that the lack of procedural consolidation observed for the WL condition in Experiment 1 and other work (e.g., Brown & Robertson, 2007a) resulted from a reduction in cortical excitability at M1 being induced from the presence of the declarative learning at a critical time point for procedural consolidation. Alternatively, despite experiencing the WL task, having previously being exposed to exercise, allowed individuals in the WL+EXE condition to maintain cortical excitability at M1 at a level close to baseline thus allowing procedural consolidation to be undertaken. Experiment 2 was designed to evaluate this possibility.

Experiment 2 included the VC, WL, WL+EXE conditions used in Experiment1 with one important modification. Single-pulse transcranial magnetic stimulation (TMS) was incorporated prior to and after practice to assess cortical excitability at M1 at key time points especially during the consolidation period.

It was expected that the behavioral outcomes from Experiment 1 would be replicated. That is, procedural consolidation would be present when SRTT learning was followed by a VC task but would be impeded when the subsequent practice involved declarative learning (WL recall). Most importantly, we anticipated that experiencing a brief bout of exercise prior to the interference induced by declarative learning would afford procedural consolidation. The innovative prediction for Experiment 2 was that cortical excitability at M1 would remain close to baseline at the conclusion of practice for both the VC and WL+EXE conditions whereas M1 excitability was expected to drop below baseline level for the WL condition at the completion of practice.

Methods

Participants

A total of 55 undergraduate right handed students were recruited as participants for Experiment 2. Thirty-five participants were included in all following reported analyses as a result of meeting the declarative knowledge requirement (i.e., < 4 elements correct in a post-experiment verbal recall test). Twenty participants were thus excluded from Experiment 2. The individuals assigned to each of the three experimental conditions in Experiment 2 did not differ as a function of age [F(2,32) = 0.69, p=0.51], body mass index [F(2,32) = 2.80, p=0.08], resting heart rate [F(2,32) = 0.91, p=0.41], heart-rate predicted maximum, [F (2,32) = 0.69; p=0.51], and heart rate reserve [F(2,32) = 0.72; p=0.50]. These data are reported in Table 2.

Table 2. Demographic (mean, SD) of all participants in Experiment 2

	N	Male	Female	Age (Yrs)	BMI	Resting Heart Rate (RHR)	HRage-predicted max (HRmax)	Heart Rate Reserve (HRR)	Declarative knowledge of SRTT
VC	12	2	10	201.17±1.85	22.03±1.55	72.25±4.70	193.88±1.30	121.63±4.44	2.83±1.19
WL	11	6	5	21.00±1.61	24.18±3.42	71.18±8.85	193.30±1.13	122.12±9.00	1.82±1.54
WL+EXE	12	7	5	20.83±1.95	24.19±2.44	69.92±4.14	193.42±1.36	124.50±4.50	1.67±1.15
Total	35	15	20	20.66±1.80	23.45±2.68	70.77±6.15	193.54±1.26	122.77±6.20	2.11±1.37

Tasks

Procedural Learning: Serial Reaction Time Task (SRTT). The protocol used to practice and test performance of the SRTT was identical to that used in Experiment 1.

Declarative Learning: Word List (WL). The protocol used to learn and test the WL was identical to that used in Experiment 1.

Declarative Task: Vowel Counting. The protocol used to view, count, and articulate the number of vowels in a nonsense string was identical to that used in Experiment 1.

Acute Bout of Exercise. The protocol used to implement a bout of moderate intensity cardiovascular exercise was identical to that used in Experiment 1.

Transcranial Magnetic Stimulation. In Experiment 2, prior to any practice of the SRTT a Magstim Rapid^2 was used to administer a single pulse of TMS over left M1 in order to elicit a motor evoked potential (MEP) at the first dorsal interosseous (FDI) muscle (see Figure 7).

The MEP was obtained by placing two electrodes (positive/negative) on the belly of the FDI muscle of the right hand and a ground electrode on the bony projection of the right wrist (see

Figure 7a). Signals from these electrodes were recorded, amplified, and filtered to determine the amplitude of the MEP. The initial task was to identify the location at left M1 that was optimal for inducing contractions in the right FDI. This was referred to as the "hotspot." Next, the lowest TMS intensity that could induce visible muscle contractions in at least 6 of 10 trials when TMS was applied at the hotspot was determined and defined as an individual's motor threshold (MT).

Prior to any practice, 30 separate single TMS pulses were administered at the hotspot at 120% of MT over a period of approximately 3-min. The average amplitude of the 30 elicited MEPs was used as an index of cortical excitability at M1 at baseline. The 30 single pulses were spaced at 10-sec intervals. This procedure was again administered immediately after the second bout of learning in Experiment 2 (see Figure 8). However in this case the stimulation protocol only involved five rather than 30 pulses at approximately 2-min intervals across a period of ~20-min. [4] This resulted in 11 additional assessments of cortical excitability at M1 during the post-practice period during which consolidation is assumed to go.

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[4] Five rather than 30 single TMS pulses were administered in this case to avoid saturation of the signal given M1 excitability was assessed over a relatively extensive period following the completion of practice.

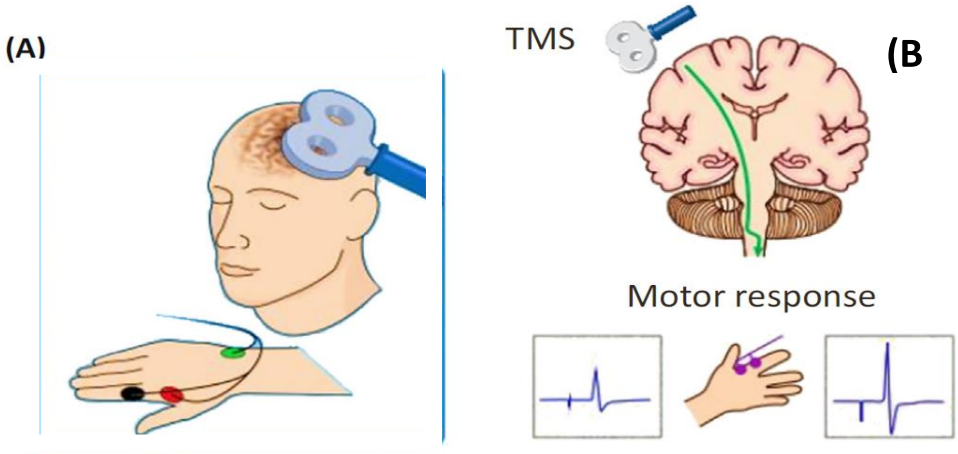

Figure 7. Cortical excitability at M1 was assessed using transcranial magnetic stimulation (TMS) (A and B). A single pulse was applied at left M1 to instigate a single motor evoked potential (MEP) of the first dorsal interosseous muscle of the contralateral hand (i.e., right-hand in Experiment 2) (C). Cortical excitability was assessed as the average of a set of pulses applied to the same location at M1 (see text for details) (figure adapted from Robertson & Takacs, 2017).

Procedure

The timeline for Experiment 2 is depicted In Figure 8. The order of events for the VC, WL, and WL+EXE conditions is identical to those used in Experiment 1. Prior to practice with the SRTT, all participants had cortical excitability at M1 assessed via single-pulse TMS (see relevant task section in the Methods). Following the relevant WL or VC tasks in each condition, single-pulse TMS was again applied to further assess cortical excitability immediately after practice and then approximately every 2-min thereafter until an additional ten measurements were made (see Figure 8). This post-practice time frame was selected because it appeared the most sensitive to changes in cortical excitability at M1 in previous work (see Tunovic et al., 2014; Ostadan, et al., 2016).

Results

Procedural consolidation and type of interference

A 3 (Condition: WL, VC, WL+EXE) x 2 (Test Block: 1, 2) ANOVA with repeated measures on the last factor for skill revealed a significant main effect of Test Block, *F* (1, 32) = 17.74, *p*<.01 as well as a significant condition x test block interaction, *F* (2, 32) = 6.17, *p*<.01. No significant difference for skill as a function of condition was observed at Test Block 1 [*F*(2,32) =0.81; *p*=0.45, VC: *M* = 48ms, SEM =7ms; WL: *M* = 64ms SEM = 7ms; WL+EXE: *M* = 49ms, SEM = 10ms, see Figure 9b], This was also true after the 6-hr wake filled interval, [*F*(2,32) =1.05, *p*=0.36, VC: *M* = 70ms, SEM = 5ms; WL: 61ms, SEM = 3ms; WL+ EXE: *M* = 79ms, SEM = 10ms]. Individuals in both the VC [*t* (11) = 3.24, *p*<.01, *M* = 21ms, SEM = 7ms] and the WL+EXE [*t* (11) = 4.18, *p*<.01, *M*= 30, SEM = 7ms) (see Figure 9b and 10) benefitted from procedural consolidation, manifest as a significant increase in skill across the 6-hr wake-filled interval. This was not the case for the individuals in the WL condition who displayed no significant change in skill from the end of training to the test administered 6-hr later [*t* (10) = 0.47, *p* = 0.65, *M*= -3ms, SEM = 7ms) (see Figure 9b and 10).

An independent t-test on WL recall for the WL and WL+EXE conditions failed to reveal a significant effect, *t*(21) = -0.63, *p*=0.54. Thus, declarative learning was similar in both the WL (*M* = 14.55 items, SEM = 0.28 items) and WL+EXE (*M* = 14.92 items, SEM = 0.50 items) conditions and extremely high.

Correlation: Procedural consolidation and declarative learning

Recall that Brown and Robertson (2007a) proposed that the extent of declarative learning following procedural learning should mediate the amount of procedural consolidation that occurs across a wake-filled interval. Despite this, we did not find a correlation between amount of declarative learning and offline gain in Experiment 1 for any of the experimental conditions. For experiment 2 we once again correlated the WL recall for each individual in the WL and L+EXE conditions with the Δ skill exhibited between TB2 and TB1. When this assessment was conducted for data from the WL condition only, there was no significant correlation (r^2=0.03, *F*=0.24, *p*=0.64, Figure 11, left panel). The same analyses performed on the data from the WL+EXE condition only was also not significant, (r^2=0.10, *F*=0.10, *p*=0.76, see Figure 11, right panel). Finally, combining these data (WL and WL+EXE) still failed to reveal a significant effect, (r^2=0.03; *F*=0.39, *p*=0.54, see Figure 12). The lack of correlation in these assessments may have resulted from the large numbers of individuals in both conditions exhibiting very high recall of the WL.

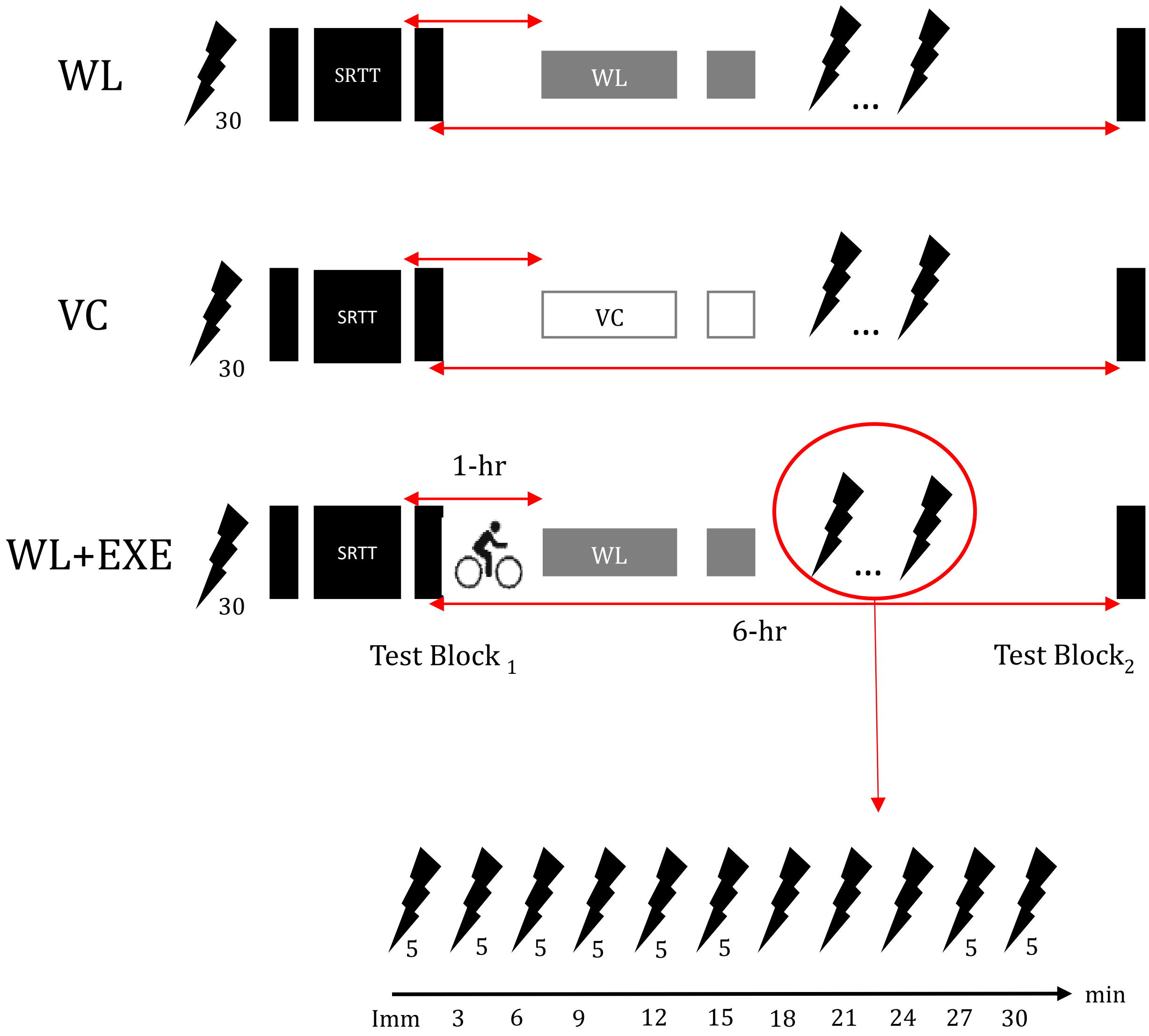

Figure 8. The same three experimental conditions included in Experiment 1: WL, VC, and WL+EXE conditions were again used in Experiment 2. The important addition to the earlier design was the inclusion of transcranial magnetic stimulation (⚡) applied both prior to any training (baseline) and after training (post) as a means of determining cortical excitability at M1. While only a single assessment of cortical excitability was made prior to practice, multiple measures (11 independent assessment were made every 3-min after training was over) were taken after practice was completed to garner insight into the potential dynamic aspect of this measure based on previous data from Tunovic et al (2014) and Ostadan et al. (2016).

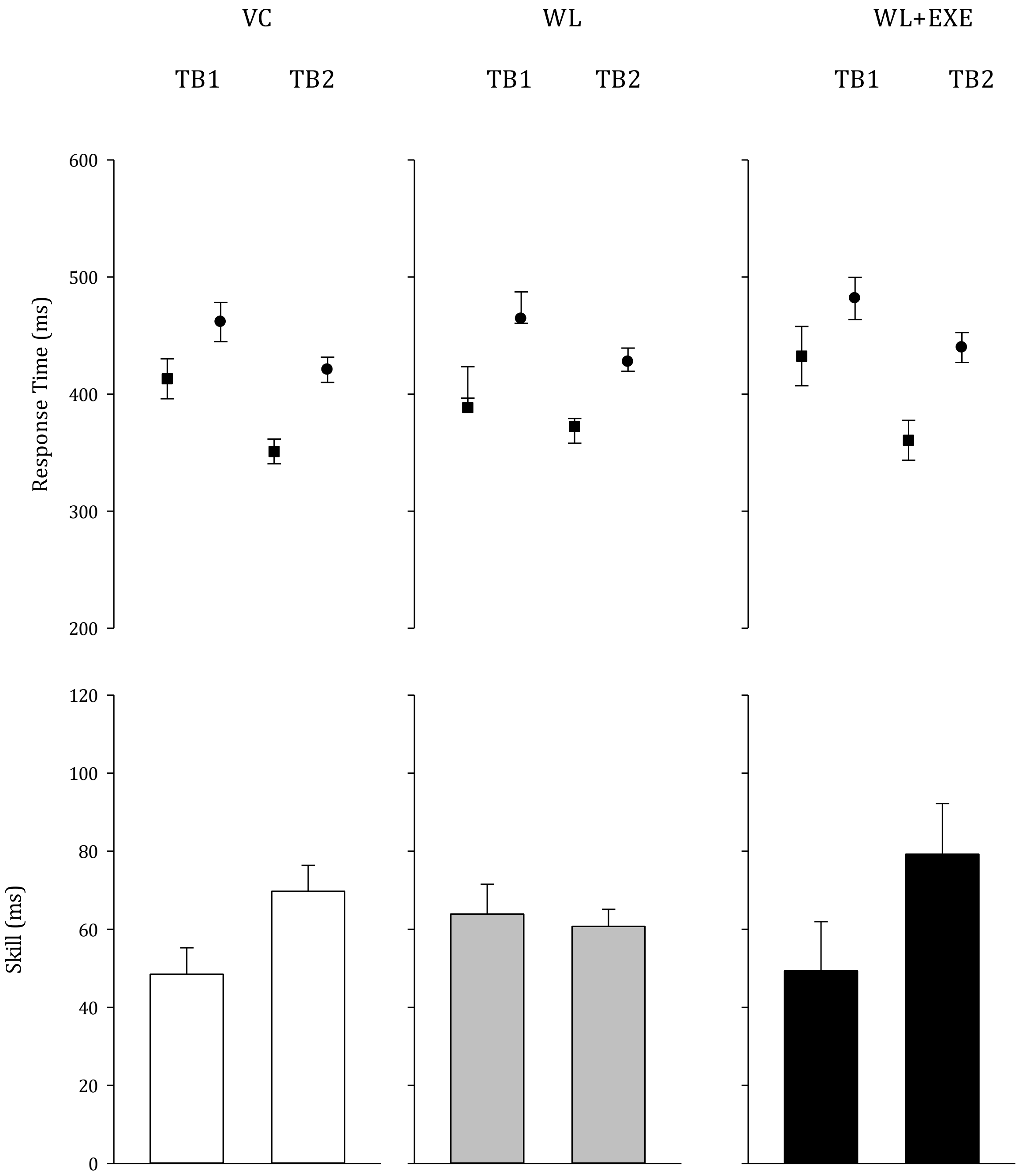

Figure 9. Mean response time (panel A) was calculated for the last 50 sequence trials (square symbol) and the 50 random trials (circle symbol) that occurred at the conclusion of practice of the SRTT (Test Block 1, TB1) and during Test Block 2 (TB2) for each of the three experimental conditions (VC, WL, WL+EXE). Skill was determined as the difference between mean response time for the sequence and random trials at TB1 and again for TB2 after 6-hr (Panel B).

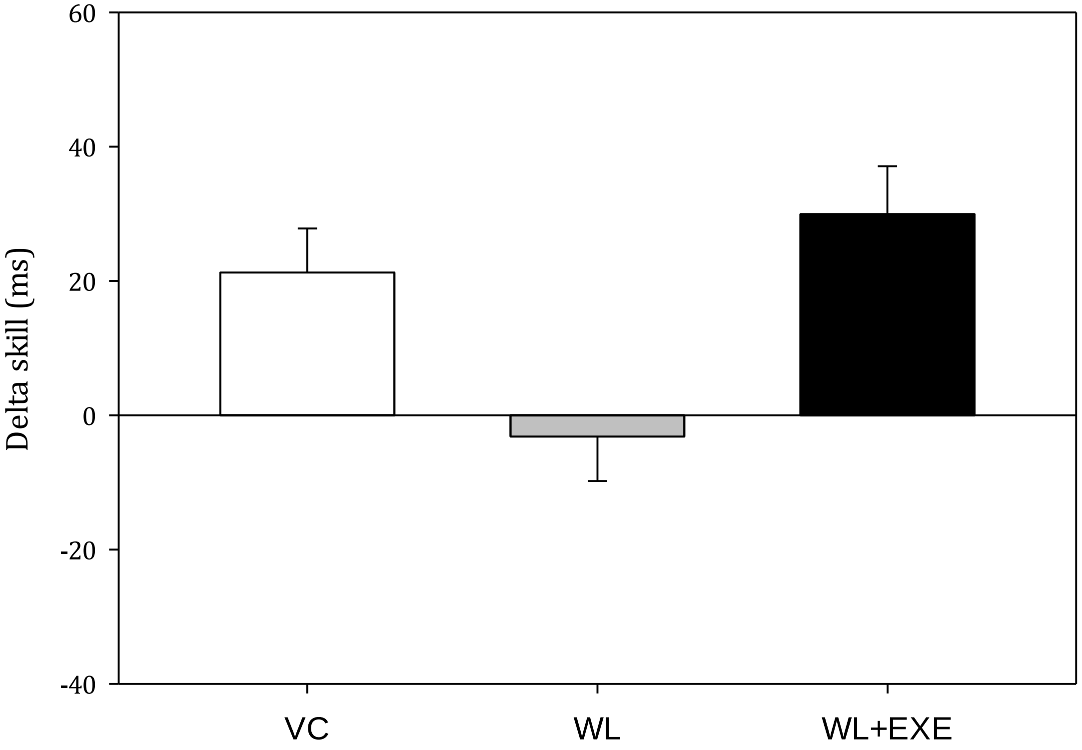

Figure 10. Mean skill was calculated at TB2 and TB1. The difference in skill (Δ skill) between these two time points reflects procedural consolidation and is present in this figure for the VC, WL, WL+EXE conditions. A larger score in this figure reflects greater procedural consolidation. In Experiment 1 both VC and WL+EXE support procedural consolidation which was not the case for the WL group.

Recall, that the intent in this work was that procedural learning unfolded in an implicit manner. Indeed, individuals that recalled greater than 4-elements of the SRTT correctly in a post-experiment verbal recall test were deemed to have explicit knowledge of the motor skill and were thus removed from the reported analyses (see Brown & Robertson, 2007). As a result of this criterion, 20 of the participants that completed Experiment 2 were eliminated. This was similar to that reported by Brown and Robertson (2007) who removed 26% of their subjects. For the participants that were included in subsequent analyses, a 3(Condition: VC, WL, WL+EXE) one-way between-subject ANOVA was conducted on the degree of declarative knowledge of the SRTT. This analysis failed to reveal a significant main effect of Condition, *F*(2,32) = 2.84, *p*=0.07. As indicated by this analysis, declarative knowledge for the SRTT at the conclusion of Experiment 2 was similar for the WL (*M* = 1.8 elements, SEM = 0.5 elements), VC (*M* = 2.8 elements, SEM = 0.3 elements), and the WL +EXE (*M* = 1.7 elements, SEM = 0.3 elements) conditions. Furthermore, there was no correlation between participants' declarative knowledge for the WL and declarative knowledge of the SRTT for the WL (r^2=0.08, *F* = 0.80, *p*=0.40) or WL+EXE (r^2=0.11, *F* =1.25, *p*=0.29) conditions. This suggest that any influence of declarative learning from learning the WL was not influencing the accumulation of declarative knowledge of the SRTT.

Cortical excitability at M1 and procedural consolidation

An important feature of Experiment 2 was describing the influence of cortical excitability at M1 on subsequent procedural consolidation. To begin this assessment, a 3 condition (VC, WL, WL+EXE) one-way between-subject ANOVA for cortical excitability at M1 (CE) at baseline was conducted. This analysis failed to reveal a main effect of condition, *F* (2,32) = 0.55, *p*=0.58. Thus, mean CE at baseline did not differ for the VC (*M* = 0.53 mV, SEM = 0.09 mV), WL (*M* = 0.61 mV, SEM = 0.08 mV), and WL+EXE (*M* = 0.54, SEM = 0.04 mV) prior to any training occurring.

Tunovic et al., (2014) reported that the % change in normalized CE from baseline shortly after practice was complete (i.e., at 6-min) was a critical determinant of eventual procedural consolidation. A 3 (Condition: VC, WL, WL+EXE) x 11 (Time: 1-11) ANOVA with repeated measures on the last factor was conducted on the % change in the normalized CE from baseline. This analysis failed to reveal main effects of Condition *F* (2, 31) = 0.93, *p* =.41, Time, *F* (10,310) = .94, *p*=.50, or a Condition x Time interaction, *F* (20,310) = .93, *p*=.54 (see Figure 13). There was one time point at which exercise seemed to have a large impact on the % change in the normalized CE from baseline (highlighted in Figure 13). We targeted this interval with a 3 (Condition: VC, WL, WL+EXE) one- way between factor ANOVA. This analysis also failed to reveal a significant main effect of Condition, *F* (2, 31) = 1.73, *p* = .19. It's worth noting that the % change in CE from baseline for the VC (*M* = 0.24, SEM = 0.10), WL (*M* = 0.16, SEM = 0.14), and WL+EXE (*M* = 0.77, SEM = 0.38) in the hypothesized order as was the case in most other time points.

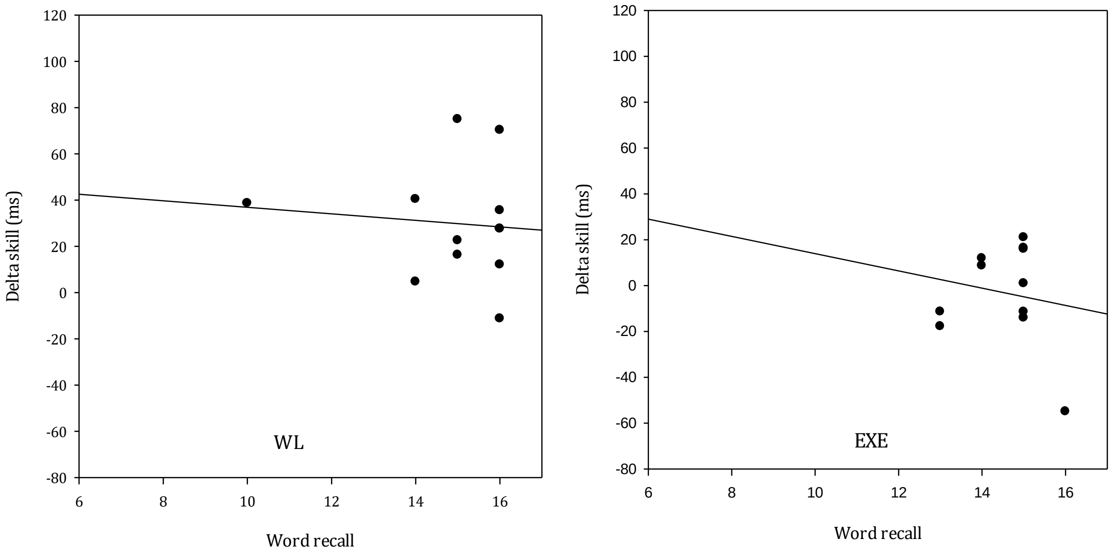

Figure 11. The relationship between the change in skill at TB2 and TB1, that is, Δ skill which reflects procedural consolidation, and performance on the WL recall test for the individuals in the WL condition only is displayed. This relationship was not significant (left panel). The relationship between the change in skill at TB2 and TB1, that is Δ skill which reflects procedural consolidation, and performance on the WL recall test for the individuals in the WL+EXE condition only. This relationship was not significant (right panel).

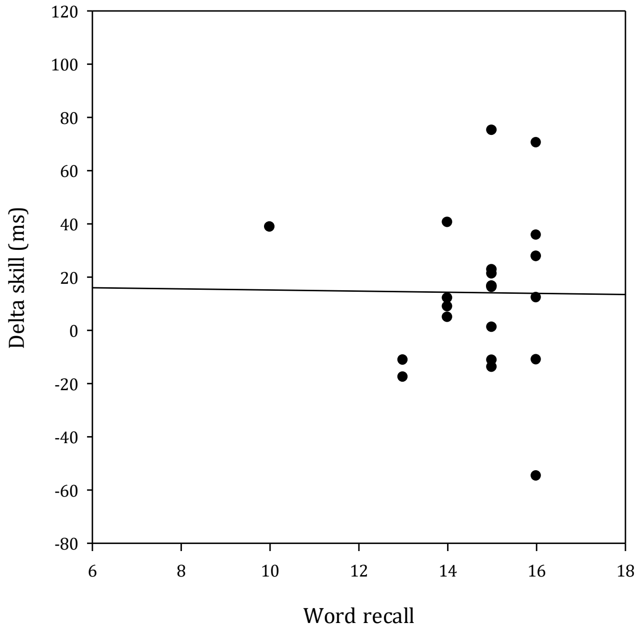

Figure 12. The relationship between the change in skill at TB2 and TB1, that is, Δ skill which reflects procedural consolidation, and performance on the WL recall test for all of the individuals in the WL and WL+EXE conditions is depicted. This relationship was not significant.

To probe this issue further we used one additional measure that Ostadan et al. (2016) argued more accurately reflects global changes in excitability in the post-practice period. This involved calculating the area under the normalized MEP curve (AUC) for each individual. In essence, the normalized CE measurements obtained for each time point (i.e., Imm-20 min, see Figure 13) were used to estimate the AUC using the trapezoidal function (trapz(y)) in Matlab. This function approximates the integration over an interval by breaking the area down into trapezoids, Ostadan et al. proposed that this approach more accurately captures the dynamic nature of excitability over time. The AUC for each individual was submitted to a 3 (Condition: VC, WL, WL+EXE) one-way between factor ANOVA. This analysis failed to reveal a main effect of Condition, F (2, 31) = 0.88, *p*=0.42 indicating that mean AUC across conditions was similar (VC: *M* = 12.76, SEM = 1.02; WL: *M* = 12.02, SEM = 1.25; WL+EXE: *M* = 14.96, SEM = 2.20) (see Figure 14).

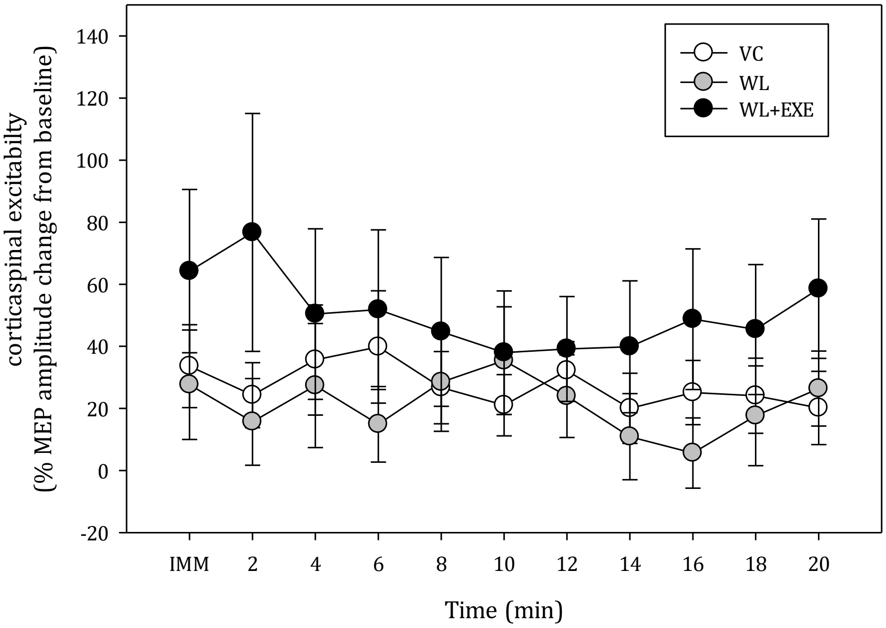

Figure 13. Mean % change in normalized cortical excitability from baseline for individuals in each of the experimental consolidation (VC, WL, and WL+EXE) immediately after practice was complete and every 2-min from that point for 20-min. The highlighted section was singled out for separate analysis to examine if the WL+EXE condition exhibited significantly greater % change in normalized CE from baseline compared to VC and WL conditions.

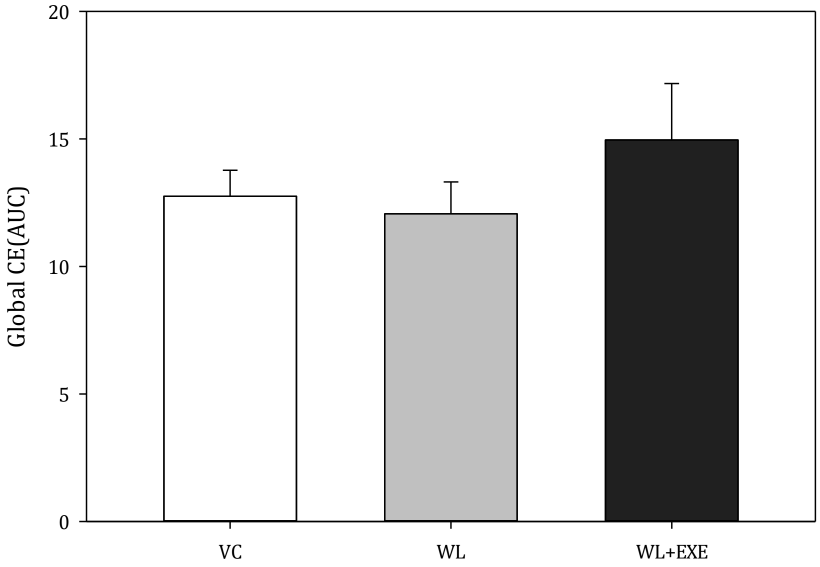

Figure 14. Mean AUC (a global measure of cortical excitability across the first 20-mon post training) for each of the experimental conditions (VC, WL, WL+EXE). While the WL+EXE revealed larger mean AUC the differences in mean AUC as a function of condition did not differ significantly.

Correlation: Cortical excitability at M1 and procedural consolidation

Despite the lack of differences in measures of cortical excitability during the post-practice period across experimental condition (VC, WL, WL+EXE) the relationship between normalized cortical excitability at 2-min post training and offline gain was examined. These analyses failed to reveal a significant relationship for the VC ($r^2 = 0.01$, F=0.10, p=0.76), WL (r^2= 0.01, F=0.05, p=0.82), and the WL+EXE (r^2= 0.10, F=1.06, p=0.33) conditions. A similar set of analyses were conducted to evaluate potential relationships between mean AUC and procedural consolidation. Again, no significant correlations were revealed for VC ($r^2 = 0.03$, F=0.24, p=0.63), WL (r^2= 0.12, F=1.27, p=0.29), and WL+EXE ($r^2 = 0.19$, F=2.30, p=0.16) conditions (see Figure 15 for example of these correlations). Clearly the magnitude of cortical excitability at M1 does not predict the eventual offline gains that are observed.

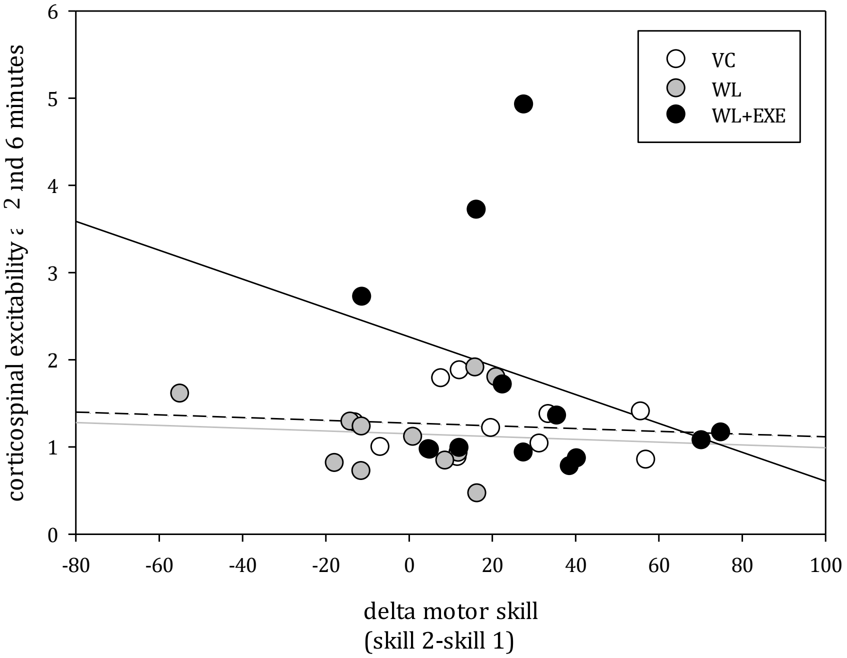

Figure 15. Mean AUC and offline gain was correlated as a function of each experimental condition VC, WL, WL+EXE conditions. No significant relationships emerged. This was also true when normalized cortical excitability at 2-min post training was correlated with offline gain. Cortical excitability did not predict the resultant offline improvement.

Discussion

Experiment 2 was designed with two key issues in mind. First, it was important to replicate the beneficial influence of an acute bout of exercise for procedural consolidation reported in Experiment 1. The second issue was to consider if changes in cortical excitability, recorded at M1, played a role in the emergence of procedural consolidation (tunovic et al., 2014). Specifically we evaluated if cortical excitability at M1 would remain close to baseline at the conclusion of practice for both the VC and WL+EXE conditions but transiently drop below baseline level for the WL condition following the completion of practice. Breton and Robertson (2014) claim that a significant decrease in cortical excitability following motor skill practice may be a physiological signal that acts as a brake to prevent subsequent consolidation during wakefulness.

Acute exercise facilitates post-practice procedural consolidation

As was the case in Experiment 1 some individuals acquired the SRTT skill while also exhibiting considerable explicit knowledge of the motor sequence at the conclusion of the experiment. Consistent with Brown and Robertson (2007) and Experiment 1, these individuals were removed from any further analyses. For those individuals that acquired the SRTT with little explicit knowledge, procedural consolidation was again evident across the wake period (see VC condition in Figure 10). As expected, being exposed to a bout of declarative learning immediately after practicing the SRTT, resulted in disruption of procedural consolidation reflected in offline gains being absent at the 6-hr test.

Most importantly, introducing a brief bout of moderate-intensity cardiovascular exercise after practice of the SRTT supported the re-emergence of offline gain despite the inclusion of declarative learning in the form of WL recall at the same time point as in the WL condition. Exercise protected the newly acquired motor memory from interference allowing consolidation to unfold uninterrupted after completing the bout of declarative learning. These data, taken together with earlier findings (Roig, et al., 2012; Rhee et al., 2016; Jo et al., 2018), offer clear support for a role for an acute bout of exercise as a means to facilitate the ongoing development of a motor memory.

Changes in cortical excitability and procedural consolidation

Tunovic et al. (2014) proposed that a decline in cortical excitability (CE) at M1 just after practice of a procedural skill was complete, presumably when consolidation is being implemented, is a signature for disruption in this critical memory process, resulting in no offline gain. In contrast, maintaining CE at a level congruent with that displayed at baseline (i.e., prior to practice in Tunovic et al.) was associated with the procurement of offline improvement. It was this account that was examined in Experiment 2. Specifically, it was hypothesized that the lack of procedural consolidation in the case of the WL condition was a consequence of the additional declarative activity down regulating M1 excitability. By contrast, the inclusion of exercise prior to declarative learning was proposed to maintain excitability at M1 at a level more congruent with that expected in the VC condition. The notion that an acute bout of exercise might have the capacity to induce an increase in cortical excitability has been demonstrated in the past (see Ostadean, et al., 2016).

The evaluation of CE at M1 for each of the experimental conditions was addressed in a number of different ways, each having been used independently in previous work that has focused on M1 excitability and consolidation and/or exercise (see Tunovic et al., 2014; Ostadan, et al., 2016). The change in CE at M1 (normalized to baseline) across all times points assessed during the first 30-min of the post-training period seemed the most pertinent initial evaluation. As can be seen in Figure 13, exercise did appear to lead to the largest increase in CE at M1 but this was not significantly different from that observed for the VC or WL conditions. Moreover, the anticipated decline in CE for the WL condition, compared to the VC condition, did not emerge. This global assessment of CE during the initial post-practice period was supplemented using a different approach that utilized the AUC measure adopted by Ostaden et al. They argued that the AUC measure more accurately reflects global excitability across a fixed time period. As was the case for the % change in the normalized to baseline CE measure, mean AUC also indicated that CE was largest for individuals exposed to exercise but the magnitude of this effect was not significant. Again, mean AUC or global CE during the first 30-min post practice was very similar for individuals in the VC and WL conditions (see Figure 14). Taken together, these data then converge on the conclusion that the absence (WL condition) and return (WL+EXE condition) of procedural consolidation was not a result of predictable changes in CE at M1.

Tunovic et al.'s account of the relationship between CE at M1 and procedural consolidation was predicated on the measurement of CE at a single time point following practice, that is, at post 6-min. Specifically, Tunovic et al reported that it was at this time point only that CE was reduced or maintained at a level similar to baseline which resulted in offline loss or gain respectively. To examine if there was a specific time point early in the post-practice period we extracted the change in CE at M1 at 2-min. It was here, as in Tunovic et al., that the largest differences in this measure appeared to surface. Interestingly, at this time frame, as well as many others, the magnitude of CE changes observed was consistent with our original hypothesis. That is the WL was expected to lead to a decline compared to the VC and WL+EXE. Nonetheless, these difference failed to meet conventional standards of significance (i.e., p=.19). It is also worth noting that none of the experimental conditions used in Experiment 2 actually resulted in CE at M1 that was less than baseline (see Tunovic, et al., 2014, Breton & Robertson, 2014, 2017). Rather the noted differences between the experimental conditions were always with respect to the extent to which CE increased beyond the baseline level. These data then do nothing to suggest our earlier conclusion that the absence (WL condition) and return (WL+EXE condition) of procedural consolidation in the form of offline gain was a not a result of predictable changes in CE at M1, is incorrect.

CHAPTER IV

SUMMARY

Two experiments were conducted to examine the impact of a brief, moderate bout of cardiovascular exercise on the development of a motor memory that was initially acquired implicitly. A number of key findings emerged with respect to (a) the importance of exercise for supporting procedural consolidation, (b) exercise as a means of mediating physiological states critical for consolidation, and (c) the manner in which declarative and procedural learning systems de-couple in order to foster procedural consolidation.

Exercise as a contributor to procedural consolidation

Probably the most robust finding across the two experiments presented herein is the positive impact the introduction of an acute bout of exercise had on offline enhancement presumably by supporting procedural consolidation. Numerous studies have been conducted in recent years presenting data congruent with this general statement (Roig, Nordbrand, Geertsen & Nielsen, 2013; Roig, Thomas, Mang, Snow, Ostadan, Boyd, & Lundbye-Jensen, 2016). Many of them however are plagued by small details either in the way of a peculiar finding or design feature that questions the claim that exercise offers a unique and independent contribution to the development of motor memory and in particular via improving the implementation of post-practice consolidation. For example, many studies have failed to eliminate sleep from retention intervals (Roig et al., 2012; Rhee et al., 2016) when evaluating the importance of exercise-supplemented practice conditions, leaving open the possibility that exercise might operate in concert with specific sleep processes that have a rich history in the consolidation literature in bringing about more effective offline processing (Walker et al., 2003; Bottary, Sonni, Wright, & Spencer, 2016). Alternatively, it is hard to understand, without contemplating a key role for sleep, how the impact of exercise for offline gain is greater after 7-days as opposed to 24-hr (Roig et al., 2012).

The data present herein are the most clear to date arguing for an independent contribution from exercise to procedural consolidation. Implicitly learned motor skills have been reported to exhibit consolidation over a wake period resulting in offline enhancement. The enhancement has been shown to be susceptible to interference in numerous previous studies from both the acquisition of alternative skills or via non-invasive brain stimulation being applied at key neural sites to perturb consolidation. This was the case in the present work in which declarative learning was the alternative activity that turned out to be very powerful form of interference essentially eliminating all offline gain. Yet, placing a brief bout of exercise provided sufficient impetus for procedural consolidation to be implemented leading to the return of the offline gain despite the learner having just completed a period of successful declarative learning. While these data do little in the way of explaining how exercise is mediating the consolidation process it is important to not overlook the potential potency of exercise as an adjunct to training as a possible means of improving the development of newly minted, often quite labile, motor memories.

Exercise as a means of mediating physiological states critical to consolidation

An extensive literature has developed detailing the importance of establishing specific physiological states in order to support the execution of important memory processes for retention of motor skills. Much has been made of the role played by NREM2 sleep stage for supporting the consolidation of explicit sequence learning. Specifically, it has been demonstrated that it is during this stage a reliable increase in the number of sleep spindles occur in the EGG signal that is highly predictive of subsequent offline gain. Perturbation of the sleep spindles during this part of the sleep cycle leads to poor explicit sequence performance at delayed tests (Bottary et al., 2016; Walker, 2005).

Breton and Robertson (2014, 2017) proposed that inhibition of cortical excitability at M1 shortly after motor skill learning serves as a physiological signal that impedes subsequent procedural consolidation. Across a number of experiments Tunovic et al. attenuated or eliminated this ‘stop’ signal using theta-burst protocols with TMS and revealed concomitant loss or gains in offline enhancement respectively. On the basis of these data, avoiding a transient reduction in M1 excitability following a period of training with a motor skill is crucial in securing ongoing gains via offline processing.

Given acute exercise has been reported to change M1 excitability in the absence of motor skill practice (e.g., McDonnell, Buckley, Opie, Ridding, & Semmler, 2013) as well as following motor training (Ostadan, et al., 2016), it was not difficult to entertain the possibility that exercise might also function to do the same in the present experiment. More specifically, it was hypothesized that experiencing interference from declarative learning, which was associated with the loss of offline gain, may have suffered from a down-regulation of M1 excitability as a result of the additional learning. It may also be important that this learning was unique from the procedural skill in order for this to happen. By introducing exercise prior to this activity, M1 excitability might in a sense be “primed” such that subsequent handling of the additional learning load did not reduce M1 excitability to the point it hindered (i.e., dropped below baseline levels, see Tunovic et al., 2014) consolidation of the prior procedural skill. Of course, an implicit assumption with this account was that a non-learning alternative activity (e.g., VC) would not modify excitability beyond baseline thus supporting consolidation.

Exercise following declarative learning interference induced a sizeable increase in M1 excitability beyond that observed at baseline while the individuals that dealt with vowel counting task avoided the transient lowering of cortical excitability Breton and Robertson claim disrupt subsequent offline consolidation. These data are as expected. However, while exposure to just a bout of declarative learning following acquisition of the SRTT was associated with a smaller increase in M1 excitability, this difference was not reliable, yet offline gains were eliminated. It is difficult to reconcile this finding with Breton and Robertson's proposal that a temporary reduction in cortical excitability beyond that experienced prior to training is an indicator of later problems with consolidation. The data presented herein provide a clear example of M1 excitability been maintained, yet performance after six hours displays no enhancement. Clearly some other neuro-plastic events must also be occurring beyond just changes in the current status of M1 to account for the present findings.

Using declarative and procedural systems during procedural consolidation

The findings of Brown and Robertson (2007a, b) as well as those reported in Experiment 1 and 2, revealing that a declarative learning task can disturb the evolution of memory for a procedural skill, challenged prevailing thinking that the declarative and procedural systems operate independent of one another. The latter position has a long historical standing on the basis of findings from individuals with certain disease states, such as Alzheimer's disease, demonstrating the patients' inability to learn and recall facts while exhibiting considerable capability to learn new skills. Alternatively, in Huntington's disease for example, the patient learns and recalls facts but struggles to acquire new skills. More recently, evidence from functional imaging studies, has revealed anatomically distinct neural circuits deemed responsible for overseeing retention of declarative and procedural memories (see Figure 1) (Robertson, 2012).

Brown and Robertson argued that the apparent independence of these systems that are central to acquiring knowledge is replaced by interdependence if certain circumstances exist. For Brown and Robertson such circumstance pertained to particular brain states which in today's neuroscience parlance may include functional or resting state connectivity profiles. Robertson and Takacs (2017) alluded to a variety of factors that might contribute to creating alternative "states" each of which might have a vastly different consequence for the consolidation of procedural skills. We have already discussed one dichotomy – sleep and wake cycles – that clearly exert distinct influences on the implementation of consolidation and associated offline improvement. Others might include: development stage, incentive, and of course exercise (see Robertson & Takacs, 2017).

Biological plausible models to account for the performance of individuals in the VC and WL conditions across a wake period have been forwarded by Brown and Robertson and elaborated by Robertson (2009) (see Figure 1 in the introduction). Those in the VC condition are assumed to exhibit procedural consolidation because the components (MTL, IPL, neocortex) of the declarative system do not need to be recruited. In contrast, activating neural sites necessary to conduct a bout of declarative learning while attempting to engage procedural consolidation either demand some coordination for the circuit to use common sites (e.g., DLPFC) or have less access to a share neural sites (MTL). Either outcome likely means procedural consolidation suffers and the outcome is less offline gain.

As noted, introducing exercise led to the functional benefit of offline gain in keeping with individuals that encountered vowel counting and significantly superior to that observed for the individuals that had to use the declarative system. However, the findings from Experiment 2 revealed that this was accomplished without changing the readiness of M1 as excitability at this site was not differentially impacted by the inclusion of exercise. Thus, the role of exercise doesn't appear to involve priming a key site in the circuitry specific to procedural consolidation which presumably would be advantageous when attempting to develop a motor memory. At this point it is unclear as to how exercise is contributing to this novel finding. Clearly, going forward, delineating how exercise imparts its influence will needs to be a priority. One obvious possibility is that exercise works in a manner similar to sleep in that it de-couples features of these systems. In the case of Brown and Robertson's models this means eliminating the contribution form an executive (e.g., DLPFC) or forcing consolidation to occur in unique circuits. While this appears the most parsimonious place to begin to probe how exercise supports procedural consolidation, it is important to note that recent work by Jo et al. suggest that sleep and exercise offer distinct contributions to consolidation.

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