Neural correlates of sleep-related consolidation of memory for cognitive strategies and problem-solving skills

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Abstract

A leading theory for why we sleep focuses on memory consolidation — the process of stabilizing and strengthening newly acquired memories into long-term storage. Consolidation of memory for cognitive strategies and problem-solving skills is enhanced as compared to a period of daytime wakefulness. Importantly, sleep preferentially enhances memory for the cognitive strategy *per se,* over-and-above the motor skills that are used to execute the strategy. Although it has been known for some time that sleep benefits this type of memory, it is not known how this process unfolds during sleep, or how sleep transforms this memory trace in the brain.

Sleep is classified into rapid eye movement (REM) sleep and non-REM (NREM) sleep. The role of REM sleep for consolidation of memory for problem-solving skills remains controversial. In addition, little attention has been paid to the possible distinct roles of phasic REM sleep (*i.e.,* when bursts of eye movements occur) and tonic REM sleep (*i.e.,* the presence of isolated eye movements and the absence of eye movement bursts). REM sleep might favour procedural memory consolidation for cognitive strategies and problem-solving skills, and the specific role of REM sleep in this process might be discernible only by differentiating between phasic and tonic REM states.

In addition, fMRI studies have revealed that sleep-related consolidation of the memory trace for simple motor procedural skills is associated with strengthened activity of, and functional connectivity between, key memory-related brain areas (*i.e.,* hippocampal, striatal, and neocortex). However, fMRI techniques have not yet been employed to investigate sleep-related consolidation of procedural memory for cognitive strategies and problem-solving skills.

Participants (n=60) performed a procedural memory task involving a cognitive strategy while undergoing functional magnetic resonance imaging (fMRI) before and after a condition of Sleep, Nap, or Wake. Those in the Sleep and Nap condition underwent polysomnography (PSG) to further study the learning-related changes in sleep macrostructure and microstructure. This thesis not only shows that a period of sleep or a nap afford a greater benefit to memory consolidation of a procedural strategy than a period of wake, but more specifically: In **Study 1**, during sleep, phasic REM sleep theta power was directly associated with overnight improvement on the task, whereas tonic REM sleep sensorimotor rhythm power was greater following a night of learning compared to a non-learning control night. In **Study 2**, we show that distinct hippocampal, striatal, and cortical areas associated with strategy learning are preferentially enhanced. **Study 3** reveals that the functional communication among these brain areas is greater following sleep compared to a daytime nap or day of wakefulness. Sleep-related changes in brain activation and functional connectivity were both correlated with improved performance from before to after a period of sleep.

Overall, findings from this thesis support the benefit of sleep at the behavioural and systems level for consolidating procedural memory involving cognitive strategies used to solve problems. The findings suggest that the multifaceted nature of REM sleep must be examined separately by its phasic and tonic states, to identify the active role of REM sleep for consolidating memory. Further, the consolidation of the memory trace is reflected through activation of, and communication between hippocampal, striatal, and neocortical brain areas. In summary, this thesis shows that sleep actively consolidates memory for cognitive strategies and problem-solving skills.

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Preface

Ethics Statement

All work in this thesis was approved by the University of Ottawa Research Ethics Board and the Research Ethics Board at the Royal Ottawa Mental Health Research Institute.

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This thesis is submitted in article format. At the time of submission of the thesis, all three articles have published. All studies have permission by the respective articles' publishers to be republished for the purpose of this thesis. Minor changes have been made to fit the format and of the thesis.

Contributions of Authors

All studies presented in this thesis are unique contributions, and represent the thesis work conducted by Nicholas Vandenberg, with guidance and supervision from Dr. Stuart Fogel. This work would not be possible without the combined efforts of several past and present members of Dr. Stuart Fogel's research lab.

Study 1: Eye movements during phasic *vs*. tonic REM sleep are biomarkers of dissociable EEG processes for the consolidation of novel problem-solving skills (Published in *Sleep*, 2023)

Nicholas Vandenberg designed the study, collected and analyzed the data, and wrote the manuscript. Aaron Gibbings processed the data. Daniel Baena-Perez processed the data. Alyssa Pozzobon assisted in data collection and data processing. Julia Al-Kuwatli assisted in data collection and administrative duties. Laura Ray assisted in data analysis and editing of the manuscript. Stuart Fogel designed the study, supported data analysis, and supported the writing and editing of the manuscript.

Study 2: Sleep enhances consolidation of memory traces for complex problem-solving skills (Published in *Cerebral Cortex,* 2021)

Nicholas Vandenberg, collected and analyzed the data, and wrote the manuscript. Alyssa Pozzobon shared in data collection, administrative duties, and editing of the manuscript. Zhuo Fang supported data analysis. Julia Al-Kuwatli shared in data collection and administrative duties. Balmeet Toor shared in data collection. Laura Ray supported data analysis, administrative duties, and editing of the manuscript. Stuart Fogel designed the study and supported students in data analysis and writing of the manuscript.

Study 3. Sleep strengthens resting-state functional communication between brain areas involved in consolidation of problem-solving skills (Published in *Learning & Memory,* 2023)

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List of Abbreviations

dlPFC	Dorsolateral Prefrontal Cortex
EEG	Electroencephalography
EMG	Electromyography
EMG	Electromyography
EOG	Electrooculography
fMRI	Functional Magnetic Resonance Imaging
GABA	Gamma Aminobutyric Acid
NREM	Non-Rapid Eye Movement
OFC	Orbitofrontal Cortex
PET	Positron Emission Tomography
PGO	Ponto-Geniculo-Occipital
PSG	Polysomnography
REM	Rapid Eye Movement
ROI	Region of Interest
RSFC	Resting-State Functional Connectivity
SHY	Synaptic Homeostasis Hypothesis
SMA	Supplementary Motor Area
SWS	Slow Wave Sleep
TRN	Thalamic Reticular Nucleus

Chapter 1: General Introduction

1. General Overview

The Jesuit College of Henri IV in La Flèche, France, permitted at least one bright student to sleep in on school day mornings (Wollaston, 1964). It is possibly more than a coincidence that this student, René Descartes, would later claim to have understood the scientific method in a series of three dreams (Baillet, 1691; cited in Feuer, 1963; Withers, 2008). Throughout history, several important discoveries have anecdotal and circumstantial claims that the solutions to problems were realized following a period a sleep, including chemist August Kekulé's discovery of Benzene, and Dmitry Mendeleev's creation of the periodic table of elements (Baylor, 2001). This thesis focuses on how the sleeping brain facilitates novel solutions to problems.

An overview of sleep will first be provided, with a particular focus on how the sleeping brain can be recorded using gold-standard approaches such as electroencephalography (EEG). This will provide background on the stages of sleep and the neural oscillations that characterize each sleep stage. The putative functions of these neural oscillations are described, which collectively provide compelling reasons for why sleep is important. One leading hypothesis for why sleep is important, involves a benefit to memory consolidation. The subsequent section will therefore describe types of memory, and their neural correlates.

Having contextualized sleep and memory separately will enable an exploration into theories of sleep-related strengthening and stabilizing of memory — a process known as *memory consolidation*. Considerable progress has unraveled how sleep consolidates cognitively simple procedural motor skills. One shortcoming of our understanding of sleep-related memory consolidation is in regard to procedural memory consolidation of *strategies or skills needed to solve problems*, which is the focus of this thesis. Through behavioural and neuroimaging techniques, this thesis will advance our understanding into how the sleeping brain consolidates procedural memory for cognitive strategies and problem-solving skills.

2. An Overview of Sleep Stages and Neural Oscillations

The process of how we sleep is well-understood, largely indebted to advances in research methodology from the early to mid-twentieth century (Aserinsky & Kleitman, 1953; Berger, 1929; Davis et al., 1937, 1939; Loomis, Harvey, & Hobart, 1935; Loomis, Harvey, Hobart, et al., 1935; Rechtschaffen & Kales, 1968). Some of the first EEG recordings observed changes in neural rhythms that were unique to sleep (Berger, 1929). Despite the widely held belief that sleep was a period of inactivity, these early observations clearly showed that the sleeping brain was not simply quiescent or 'shut-down'. Rather, the sleeping brain was a distinct state of lowered behavioural responses and sensory processing, but, paradoxically, an active state with unique EEG characteristics.

2.1. Endogeny of EEG. EEG records the regional summation of extracellular local field potentials from underlying cortical areas that manifest as neural oscillations. These neural oscillations reflect, at the cellular level, the extracellular current and fluctuating membrane potential of neurons (Buzsaki et al., 2012). Various factors can all contribute to the observed extracellular current, including synaptic activity, calcium spikes, and fast action potentials, all of which vary in creating discernible extracellular activity (Buzsaki et al., 2012). Synaptic activity produces a weak current, but is slow in duration, highly synchronous, and is therefore a primary source of EEG-detectable activity. In a superficial sense, EEG reflects scalp-recorded oscillatory activity of neuronal ensembles.

2.2. Polysomnography and Sleep Architecture. Neural oscillations are highly organized, displaying distinct patterns of neural up- and down-states during different phases of sleep (Navarro-Lobato & Genzel, 2019). Unsurprisingly, each phase of sleep is consistent between individuals, and is categorized into distinct canonical stages (Silber et al., 2007). In addition to EEG, electrodes placed near the eyes (electrooculography; EOG) and facial muscles (electromyography; EMG) record other characteristic features of sleep, which together form polysomnography (PSG). In humans, sleep stages are visually scored in 30-second epochs as one of four stages, according to a standardized system

(Rechtschaffen & Kales, 1968). This system remains the universal standard, and has undergone recent revision (Iber et al., 2007; Silber et al., 2007).

Sleep is generally categorized as either Rapid Eye Movement (REM) or Non-Rapid Eye Movement (NREM) sleep. NREM sleep comprises NREM1, NREM2, and NREM3 (also known as slow wave sleep; SWS). The architecture of sleep has a highly organized, predictable structure, whereby NREM-REM periods generally occur every 90 minutes. These cycles typically involve a gradual and systematic descent from NREM1 to NREM2, into deeper NREM3, then a return to NREM2 and finally transition into REM sleep at the end of each cycle. The first half of the night is when the majority of NREM3 occurs. REM periods progressively increase in duration over the course of the night, and therefore, the last half of the night is where most REM sleep occurs. See **Table 1** for a summary of the notable characteristics of each sleep stage, and for an overview of the associated neural substrates.

Table 1. Substrates, roles, and functions of key sleep oscillations.

Oscillations	Sleep Stage(s)	Substrates and Role	Proposed Function
Sleep Spindles	NREM2 NREM3	*Thalamic Reticular Nucleus* • Substrate • Coordination *Cortex* • Substrate • Modulate Spindles *Hippocampus* • Timing • Coordination	• Sleep Quality • Sleep Maintenance • Cognitive Function • Memory Consolidation
Slow Waves	NREM2 NREM3	*Thalamic Reticular Nucleus* • Substrate • Regulation • Synchrony • Cortical Propagation	• Sleep Homeostasis • Synaptic Recalibration • Memory Consolidation
Rapid Eye Movements	REM	*Pons* • Substrate • Muscle Atonia • Eye Movements *Thalamic Reticular Nucleus* • Modulate Eye Movements *Occipital Cortex* • Modulate Eye Movements	• Emotion Regulation • Cognitive Development • Restoration • Memory Consolidation

2.3. Wake and Sleep Onset. During wake, EEG typically shows low amplitude, desynchronized fast oscillations (>= 16 Hz) called beta activity. Prior to sleep onset, eyes closed EEG is characterized by slower rhythmic oscillations (8–12 Hz) called alpha activity. Although indicative of deep relaxation and drowsiness, the presence of alpha still signifies wakefulness.

2.4. NREM 1 Sleep. The transition from wake to sleep occurs once alpha subsides. During this time, alpha activity slows to theta (4-8 Hz) activity, which reflects an intermediate state between wake activity and sleep activity, called Stage 1, or NREM1. This stage is typically brief, often lasting up to 10 minutes in healthy individuals when first falling asleep (Carskadon & Dement, 2011).

2.5. NREM 2 Sleep. NREM2 occupies approximately 50% of a night of sleep (Carskadon & Dement, 2011). The transition from NREM1 to NREM2 is characterized by the absence of alpha activity, but the hallmark of NREM2 sleep is notably the presence of sudden bursts of activity at the sigma frequency band called sleep spindles. Sleep spindles are short (~0.5-3 second; Rechtschaffen & Kales, 1968), low amplitude (>25μV; Iber et al., 2007) bursts of neural activity (11-16 Hz) that reflect the depolarizing upstate of thalamocortical neurons (Steriade, 1995). They do not occur during NREM1 or REM sleep (Iber et al., 2007), and although they occur during NREM3, their visual appearance is obscured by high-amplitude slow wave activity.

Sleep spindles are produced by the oscillatory activity of the thalamus and the cortex (Steriade, McCormick, et al., 1993). Specifically, inhibitory gamma-aminobutyric acid (GABA) neurons in the Thalamic Reticular Nucleus (TRN) briefly suppress the continuous thalamocortical dialogue that engender slow waves (see section *2.6. NREM3 Sleep*). This inhibition induces sudden spikes of activity, which are then transmitted to the cortex, resulting in EEG-detectable spindles (Bazhenov et al., 1999; Contreras & Steriade, 1996; Steriade, 1995, 2005; Steriade et al., 1993).

Healthy sleep spindles are often nestled in the slow wave upstate (Rasch & Born, 2013; Staresina et al., 2015). In addition, high frequency (150-200 Hz) sharp-wave hippocampal ripples (most easily

detected in rodents) are nested in the troughs of spindles, which is one of the ways that spindles are thought to actively participate in memory consolidation (Helfrich et al., 2018; Latchoumane et al., 2017). Sleep spindles are thus part of a complex of slow wave-spindle-ripple events that are coupled to one another in a hierarchical structure (Navarrete et al., 2020; Staresina et al., 2015).

2.5.1. Functions of Sleep Spindles. Evidence supports a sleep-protective function for sleep spindles. For example, individuals who show more sleep spindles are less susceptible to awakenings from disruptive environmental noises (Dang-Vu et al., 2010). Reduced spindle activity is also a predictor of insomnia (Dang-Vu et al., 2015), whereas higher spindle density predicts efficacy for Cognitive Behavioural Therapy for Insomnia (Dang-Vu et al., 2017).

In addition to sleep maintenance, a considerable volume of research suggests that sleep spindles are an electrophysiological marker of cognitive function (Fang et al., 2019; Fogel & Smith, 2011; D. Smith et al., 2020; Ujma et al., 2020). Interindividual differences in intellectual ability are positively associated with stable and trait-like sleep spindle characteristics (Bódizs et al., 2005; Fogel et al., 2007; Nader & Smith, 2001, 2003; Schabus et al., 2006). More recent research has demonstrated that sleep spindles are positively related to fluid intelligence (*i.e.,* reasoning ability, and performance Intelligence Quotient; IQ), even after controlling for sleep quality and circadian chronotype (Fang et al., 2017).

Similarly, the role of sleep spindles for learning and memory has been extensively investigated. Sleep spindles are actively involved in the strengthening and stabilizing of newly formed memories (Fogel & Smith, 2011; Nader & Smith, 2003; Ulrich, 2016). As this thesis focuses on sleep and memory consolidation, an exploration of how sleep spindles are actively involved in this process will be elaborated below (See ***4.5 Active Systems Consolidation Hypothesis***).

2.6. NREM 3 Sleep. Sleep spindles also occur during NREM3 sleep, however, they are often visually obscured by ongoing slow wave activity. Slow waves (<2 Hz) propagate from anterior regions and move in a posterior direction (Massimini et al., 2004). They are the most synchronized neural oscillations across the entire cortex (Steriade, 2006; Steriade et al., 1993).

2.6.1. Functions of NREM3 Slow Waves. Ample evidence suggests that slow waves during sleep are associated with recovery from the cognitive demands of waking life — a process called sleep homeostasis (Achermann & Borbély, 2003; Borbély, 2001; Borbély et al., 1999; Born & Feld, 2012). Sleep need has been positively associated with more frequent NREM3 slow wave activity (Achermann & Borbély, 2003; Borbély, 2001), and with greater slow wave amplitude during NREM3 sleep (Borbély et al., 1999; Dijk, 1995; Dijk et al., 1990). In addition, the amplitude of slow waves decreases as the night progresses (Aeschbach et al., 1996; Borbely, 1982; Borbély et al., 2016; Riedner et al., 2007; Vyazovskiy et al., 2007).

2.7. REM Sleep. The sudden bursts of rapid eye movement (REM) activity that occur in sleeping humans were first observed by Askerinsky & Kleitman (1953), who attributed this phenomenon to what is perhaps the most widely known feature of REM sleep — its relation to vivid, story-like, often bizarre and memorable dream recall (Aserinsky & Kleitman, 1953). REM sleep was simultaneously discovered by Michel Jouvet in animals, termed *sommeil paradoxal*, in reference to its wake-like neural activity with complete muscle atonia (Jouvet, 1959; Jouvet et al., 1959). REM sleep typically follows NREM2 or NREM3, occupies about 20-25% of a full night of nocturnal sleep (Carskadon & Dement, 2011), and predominates the latter half of a night's sleep (Plihal & Born, 1997). During REM sleep, the EEG becomes desynchronized and more wake-like (McCarley & Hobson, 1975), but with accentuated theta activity (Aserinsky & Kleitman, 1953; Dement & Kleitman, 1957). Although REM sleep in rodents characterizes neural activity at the theta (4-8 Hz) band, the human analog to rodent REM theta extends

into lower frequencies (2 Hz–8 Hz; Bódizs et al., 2001; Clemens et al., 2009, 2013; Frauscher et al., 2020; Sato et al., 1997).

Rapid eye movements during REM sleep are associated with wave forms originating from the pons, geniculate nuclei, and occipital cortex, or "PGO" waves (Callaway et al., 1987; Datta & Hobson, 1994; Gott et al., 2017; Mouret et al., 1963; Peigneux et al., 2001). Positron Emission Tomography (PET) and functional Magnetic Resonance Imaging (fMRI) recordings have further elucidated the neural substrates of REM sleep. Increased activity in subcortical areas is observed, including the pontine tegmentum, putamen, and thalamus (Miyauchi et al., 2009; Wehrle et al., 2007), as well as the ventral striatum, amygdala, and the anterior cingular and insular cortices (Braun et al., 1997; Nofzinger et al., 1997). The frontal cortex shows little activity during REM (Braun et al., 1997; Laureys et al., 2000; Maquet et al., 1996; Nofzinger et al., 1997), however the dorsolateral prefrontal and orbitofrontal cortices are two exceptions (Braun et al., 1997; Nishida et al., 2005; Nofzinger et al., 1997).

2.7.1. Phasic and Tonic REM Sleep. Importantly, REM sleep is not a homogenous state. REM sleep is further subdivided into phasic and tonic REM, respectively characterized by bursts of eye movements, compared to the absence of eye movement bursts. About 20-30% of a REM episode consists of phasic events (Aserinsky, 1971). Despite clear distinctions between phasic and tonic REM sleep, surprisingly, the differentiation between the two states has received little research attention, particularly in the field of memory consolidation and information processing (Simor et al., 2020). This may be partially due to a lack of available automated rapid eye movement detection and analysis methods. Nevertheless, one study showed greater thalamocortical synchrony despite a stronger disconnect from auditory stimulation, during phasic REM sleep compared to tonic REM sleep (Wehrle et al., 2007). This led to speculations that phasic states allow for a more internally focused process, whereas tonic states are associated with relatively higher environmental responsiveness (Simor et al., 2020). Examining the differences between phasic and tonic REM states remains an intriguing avenue for further research, and

is further explored in this thesis, specifically to examine the dissociable functions of phasic and tonic REM sleep for consolidating procedural memory for cognitive strategies and problem-solving skills.

2.7.2. Functions of REM. Why might we need a state during sleep that closely resembles waking, despite the obvious disconnect from the external environment? REM sleep occurs more frequently after sufficient NREM sleep has occurred (Bes et al., 1996), suggesting that it does not serve the same homeostatic function as NREM sleep (Borbely, 1982). However, REM sleep need does accumulate with selective REM deprivation (Beersma et al., 1990; Brunner et al., 1990), suggesting a strong biological need and homeostatic drive during REM that is separate from NREM sleep. Theories on the function of REM sleep vary. They range from emotion and stress regulation (Horne, 2013; van der Helm & Walker, 2009), to brain plasticity in infants and adults (Dumoulin Bridi et al., 2015; Roffwarg et al., 1966). The revived interest in phasic *vs.* tonic REM sleep has also led to theories on distinct functions within REM sleep, for example, that phasic REM sleep facilitates the hippocampal-neocortical dialogue (Bódizs et al., 2001; Hutchison & Rathore, 2015), while tonic REM sleep is implicated in pattern separation (Montgomery et al., 2008) or contextualizing newly acquired information (Simor et al., 2020).

3. Long-term Memory Consolidation

In general, long-term memory is separated into **declarative memory** (‘*knowing what’*) and non-declarative (‘*knowing how*’) categories (N. J. Cohen & Squire, 1980). Non-declarative memory is further categorized into four subtypes (Milner et al., 1998; Squire & Zola-Morgan, 1996): 1) non-associative, *e.g*., autonomic reflexes including habituation and sensitization; 2) classical conditioning, which includes behavioural responses to unconditioned stimuli; 3) priming, including unconscious or conscious responses based on recent encounters; and 4) **procedural memory**, which is memory for skills (motor and otherwise), but also includes strategies, problem-solving skills and habits.

Evidence suggests that both declarative and procedural memories can be strengthened not only through rehearsal of the newly acquired information (*i.e*., ‘online learning’), but also when task

performance does not actively occur (*i.e.,* 'offline learning'; Dayan & Cohen, 2011). This offline learning period can happen during quiet wakefulness, or preferentially during sleep, which allows for optimal memory consolidation to take place.

3.1. Memory Consolidation and the Hippocampus. The hippocampus is central for processing both declarative and procedural memory (Anagnostaras et al., 1999; Buzsaki & Moser, 2013; Datta, 2000; Ego-Stengel & Wilson, 2010; McClelland et al., 1995; Shin et al., 2019; Winocur et al., 2005). Though traditionally associated with declarative memory only (Scoville & Milner, 1957), the hippocampus is now implicated in memory that was traditionally thought to be independent of the hippocampus, as demonstrated in rodents (Sawangjit et al., 2018), and in humans (Schapiro et al., 2019).

Even after active, 'online' learning occurs, memories can be replayed offline (Klinzing et al., 2019). Temporal replay of the neural signatures that are acquired during learning, re-occurs during offline periods of either sleep or quiet rest (Carr et al., 2011; Liu & Watson, 2020), and is optimal during sleep (Dragoi, 2020; Michon et al., 2019; Peyrache et al., 2009). Hippocampal memory replay likely involves coordination with the frontal cortex (Buzsaki, 1996; Ji & Wilson, 2007; Schabus et al., 2004). Indeed, replay in the medial prefrontal cortex (mPFC) occurs following complex rule learning (Kaefer et al., 2020), with hippocampal replay occurring either at the same time (Peyrache et al., 2009), or independent (Kaefer et al., 2020) of the mPFC. Similarly, coordination between the mPFC and hippocampus is observed during spatial learning and memory-guided decision making (Khodagholy et al., 2017; Shin et al., 2019).

3.1.1. Hippocampal-Cortical Transfer Hypothesis. The above evidence for hippocampal-prefrontal coordination is consistent with the standard hippocampal-cortical consolidation model (McClelland et al., 1995; Squire & Alvarez, 1995). This influential hypothesis suggests that newly acquired memory traces are transferred from the hippocampus to the cortex for long-term storage (McClelland et al., 1995). Evidence in humans (Scoville & Milner, 1957; Squire & Alvarez, 1995) and

animals (Winocur et al., 2005) has shown that hippocampal-dependent memories can become independent of the hippocampus as consolidation progresses. More recently, advances in neuroimaging techniques have revealed reduced hippocampal activity, and increasing cortical activity, as consolidation progresses (Grosmark et al., 2012; Poe et al., 2000; Takashima et al., 2006).

The hippocampus is therefore important for acquiring new information, and likely transfers this information to the cortex for long-term storage and retrieval. Both declarative and procedural memory require the hippocampus initially for optimal learning and subsequent transfer of long-term storage in the neocortex. However, the networks of brain areas involved in declarative and procedural memory differ, in a task-specific way.

3.2. Declarative Memory. Declarative memories consist of facts and events (N. Cohen et al., 1985; Moscovitch et al., 2006; Nadel & Moscovitch, 1997; Squire, 1992b; Tulving, 1985). Such facts and events are typically acquired through rehearsal and memorization (Graf et al., 1984; Moscovitch et al., 1986). Declarative memory is typically assessed using verbal (*i.e.,* word lists) or visual (*i.e.,* pictures, maps) identification with cued prompts or free recall (Graf et al., 1984; Shimamura & Squire, 1984).

3.2.1. Substrates of Declarative Memory. Declarative memory primarily depends on the hippocampus (Scoville & Milner, 1957; Squire, 1992a; Tulving et al., 1994), the medial temporal lobe (Davachi et al., 2003; Douville et al., 2005; Warrington, 1996), and the prefrontal cortex (PFC; Kapur et al., 1995; Nyberg et al., 1996; Schacter et al., 1996). The hippocampus is thought to retrieve easily accessible memories (Schacter, 1997; Squire, 1992b), whereas the PFC is involved when memories are not readily available (Kapur et al., 1995; Nyberg et al., 1996; Schacter et al., 1996). The medial temporal lobe is likely involved in both storage and retrieval (Davachi et al., 2003; Douville et al., 2005; Warrington, 1996), and recently, coordinated firing in both the medial temporal lobe and neocortex (*i.e.*, the temporal association cortex) was associated with verbal memory retrieval (Vaz et al., 2017). Finally,

the amygdala is implicated in consolidating emotionally salient declarative memories (Feng et al., 2018), likely through an interaction with the hippocampus (Girardeau et al., 2017).

3.3. Procedural Memory. Procedural memory includes knowledge of strategies, problem-solving skills and habits (Milner et al., 1998; Squire & Zola-Morgan, 1988). They can be developed with practice, and they are expressed through performance (Milner et al., 1998; Squire & Zola-Morgan, 1988), which normally also involves motor skills.

3.3.1. Substrates of Procedural Memory. Procedural memory putatively involves the striatum (Albouy et al., 2006; Albouy, King, et al., 2013; Debas et al., 2014; Doyon et al., 1996; Gilbert, 2001; Grafton et al., 1994; Laforce & Doyon, 2002; Lehéricy et al., 2005). Other areas that are specific to procedural motor skill learning include the thalamus and motor cortical areas (*i.e.,* the supplementary motor areas [SMA], premotor cortex, and contralateral primary motor cortex) to execute motor movements (Doyon et al., 1996; Grafton et al., 1992, 1994). Other proposed functions of the SMA include a mediating role between spatial and motor components (Hikosaka et al., 2002; Nakahara et al., 2001), as tasks often require both spatial planning components, and motor movement, to perform visuo-spatial sequences (Sakai et al., 1999). The cerebellum is involved as well, likely to support coordination and timing of these motor movements (Doyon et al., 2002; Ivry et al., 1988; Laforce & Doyon, 2002; Penhune & Doyon, 2005; Rauch et al., 1995; Spencer et al., 2003).

As newly acquired memory traces undergo consolidation, increased activity occurs in the putamen, in the parietal cortex, and in the premotor cortices (Grafton et al., 1994; Tzvi et al., 2014; Ungerleider et al., 2002). Importantly, these areas are activated only when learning motor sequences, whereas this activation is not observed for non-sequential, randomly prompted button presses (Poldrack et al., 2005; Tzvi et al., 2014). This suggests that these observed neural changes cannot be attributed to simple motor execution, and instead reflect sequence learning *per se*.

Hippocampal activation also occurs during motor sequence learning (Albouy et al., 2008; Gheysen et al., 2010; Schendan et al., 2003). Hippocampal-striatal coupling weakens as motor sequence memory consolidation progresses (Albouy et al., 2008, 2012). It is therefore thought that the hippocampus is involved during initial learning and early consolidation of procedural memories, and likely interacts with the striatum (Albouy et al., 2016; Albouy, King, et al., 2013; Fogel et al., 2016; Poldrack & Rodriguez, 2003). At the subcortical level, the hippocampus might preferentially favour the spatial component, whereas the striatum prioritizes the motor component for motor sequence learning (Albouy, Fogel, et al., 2013). This hippocampal-striatal interaction is enhanced by sleep, and will be discussed in greater detail in subsequent sections.

3.4. Procedural Memory for Cognitive Strategies & Problem-Solving Skills. The neural correlates of procedural memory that have so far been summarized are based on cognitively simple sequences of motor movements. However, motor movements are often used to acquire and execute cognitive strategies and problem-solving skills (C. T. Smith, 2001).

3.4.1. Neural Substrates of Cognitive Strategies and Problem-Solving Skills. The hippocampus, striatum, and prefrontal cortex (PFC) likely support goal-directed behaviour, rule-learning and decision-making in rodents (Ahn et al., 2019; Aoki et al., 2019; Michon et al., 2019; Pennartz et al., 2011; Peyrache et al., 2009; Pezzulo et al., 2014). A similar hippocampal-striato-cortical network is recruited when humans are engaged during problem-solving tasks (Dagher et al., 1999; Doyon et al., 1996; Rowe et al., 2001; Unterrainer & Owen, 2006; Van Den Heuvel et al., 2003). The PFC plays an additional role in planning and monitoring of task performance (Anguera et al., 2010; Grafton et al., 1994; I. H. Jenkins et al., 1994; Ungerleider et al., 2002). In addition, activity in the dlPFC is observed during the insight moment of problem solving (Tik et al., 2018).

Whereas the putamen is recruited during the learning of cognitively simple procedural motor skills (Grafton et al., 1994; Rauch et al., 1995; Tzvi et al., 2014; Ungerleider et al., 2002), the caudate is

recruited during the execution of procedural skills that require cognitive strategies, spatial planning and problem solving (Bick et al., 2019; Dagher et al., 1999; Destrebecqz et al., 2005; Doyon et al., 1996; Jueptner et al., 1997; Lappin et al., 2009; Lehéricy et al., 2005; Maquet et al., 2000; Peigneux et al., 2000; Poldrack et al., 1999; Rowe et al., 2001; Unterrainer & Owen, 2006; Van Den Heuvel et al., 2003). Specifically, the caudate has been linked to solving difficult, but not simple, versions of a sequential problem-solving puzzle (Doyon et al., 1996). Similarly, more dopamine release in the caudate is positively associated with increasing difficulty of strategy-based visuo-spatial motor sequence learning (Dagher et al., 1999). Dopamine release in both the caudate and ventrolateral putamen has occurred following spatial-motor problem solving (Monchi et al., 2006), but dopamine release in only the caudate is attributed to the spatial planning aspect (Lappin et al., 2009). Overall, the caudate, hippocampus and prefrontal cortical regions are likely responsible for consolidation of complex procedural memory, particularly for the acquisition of novel cognitive strategies and problem-solving skills.

4. Theories of Sleep and Memory Consolidation

Having discussed both sleep and memory separately, we can now examine the unique role of sleep for memory consolidation. Various hypotheses paved the way towards our present understanding of how sleep consolidates memory. The present consensus is that for most types of memory: **1)** following new learning, a period of sleep improves memory recall/performance more so than an equivalent period of wakefulness, **2)** if sleep deprivation occurs following new learning, memory performance is impaired, and **3)** changes in neural oscillations during sleep reflect the replay and reactivation of new memory traces. These converging sources of evidence have developed and reformed theories that attempt to best explain how sleep is an optimal time to preferentially and actively consolidate newly acquired memories (**Table 2**). Some of the most compelling evidence in support of these hypotheses suggests that sleep is an active contributor to memory consolidation through temporal replay and reactivation of memory

traces. The protected time afforded by sleep results in the transformation and integration of memories into long-term storage, making them more integrated and easily accessible.

Table 2. Hypotheses on the role of sleep for memory consolidation.

Hypothesis	General Role of Sleep	Role of NREM sleep	Role of REM sleep
Passive Protection	Passively protects memories from interference	No memory-specific role	No memory-specific role
Dual-Process	Memory types are consolidated during different sleep stages	Consolidates declarative memory	Consolidates procedural memory for cognitive strategies
Sequential	Alternating sleep stages complementarily process new memories	Reorganizes new memories	Actively processes and stores new memories
Synaptic Homeostasis	Homeostasis of synapses; Plasticity	Recalibrates cortical synaptic weights of previous day's information	Recalibrates subcortical synaptic weights of previous day's information
Active Systems Consolidation	Actively strengthens newly acquired memories through temporal memory replay, reactivation of memory traces, and stabilizing of memory into long-term storage	Increased activity in Sleep Spindles to actively process newly acquired memories Spindle-Slow Wave coupling reflects memory processing Neuroanatomical regions implicated in learning and memory are reactivated to consolidate memory	Pruning and reorganizing of the memory trace Promotes schema formation Promotes creativity and insight Consolidates emotionally salient memories Consolidates procedural memory for cognitive strategies and problem-solving skills

4.1. Passive Protection Hypothesis. The first study to examine sleep's relationship with memory found that participants who slept after learning words were less likely to forget them the following day

than participants who had not slept (J. Jenkins & Dallenbach, 1924). This was the first modern scientific evidence directly linking memory to sleep, albeit framed as a passive contributor in memory processing. This fit with the notion of the day whereby sleep was considered a quiescent state of oblivion and complete loss of consciousness. It was then accepted that sleep protects memories from the interference of waking life, however, sleep is now widely considered to play an active role, not a passive role, in memory consolidation (Diekelmann et al., 2009; Ellenbogen et al., 2006; Klinzing et al., 2019; Rasch & Born, 2013). Indeed, if interference occurs after post-learning sleep of a declarative task, memories are still less susceptible to forgetting than if interference occurs before the post-learning sleep period (Ellenbogen et al., 2006, 2009).

4.2. Dual-Process Hypothesis. Studies employing sleep deprivation paradigms led to the development of the *Dual-Process Hypothesis*, which stipulates that NREM sleep is important for declarative memory consolidation, whereas REM sleep is important for procedural memory consolidation (Gais & Born, 2004; Peigneux et al., 2001; Plihal & Born, 1997; C. T. Smith, 2001). In sleep deprivation paradigms, participants would be deprived of either a full or partial night of sleep after learning, when compared to participants who slept a full night. Memory was then assessed after the sleep or wake interval. Given that NREM sleep dominates the first of half of a night of sleep (see section ***2.6 NREM 3 Sleep***), whereas REM sleep dominates the second half (see section ***2.7 REM Sleep***), selective deprivation of either the first half or the second half of the night allowed for insight into whether NREM or REM sleep was involved in consolidation for different types of memory.

Following the acquisition of a simple procedural memory task, participants who underwent selective REM sleep deprivation showed no detriment to memory consolidation at retest, whereas participants who underwent NREM sleep deprivation showed impaired procedural memory consolidation (Plihal & Born, 1999; C. T. Smith & Fazekas, 1997; C. T. Smith & MacNeill, 1994; Tweed et al., 1999). Depriving participants of REM sleep following declarative learning also showed no

detriment to subsequent memory recall (Castaldo et al., 1974; Chernik, 1972; Ekstrand et al., 1971; Empson & Clarke, 1970; Lewin & Glaubman, 1975; C. T. Smith, 1993; Tilley & Empson, 1978), whereas declarative memory recall was impaired after depriving participants of NREM sleep (Plihal & Born, 1997). This established that NREM sleep was primarily involved in memory consolidation for declarative memory; though nuanced, REM sleep was then implicated in procedural memory when accompanied by a cognitive challenge in addition to the simple motor movements (Plihal & Born, 1997; Smith & Weeden, 1990; Smith & Smith, 2003; Smith, Nixon, & Nader, 2004). These studies employing selective deprivation of either NREM or REM sleep gave rise to the Dual Process Hypothesis.

Although appealing in its simplicity, special cases demonstrate a more nuanced relationship between sleep states and memory types, which cannot account for conclusions drawn from the Dual Process Hypothesis (*viz.,* NREM-declarative, REM-procedural). For example, REM sleep is also involved in declarative memory consolidation for new language acquisition (De Koninck, 1995; De Koninck et al., 1989; Koninck et al., 1990), or if memories are emotionally salient (Groch et al., 2013; Marshall & Born, 2007; Moroni et al., 2007; Nishida et al., 2009). Moreover, ample evidence suggests that NREM spindle activity is associated not only with declarative memory (Clemens et al., 2005; Fogel et al., 2007; Gais et al., 2002; Ruch et al., 2012; Schabus et al., 2004; Schmidt et al., 2006; Wolansky et al., 2006), but also with improved performance for procedural motor skills (Barakat et al., 2013; Boutin et al., 2018; Fogel et al., 2001, 2007; Fogel & Smith, 2006; Holz et al., 2012; Korman et al., 2007; Laventure et al., 2016; Lustenberger et al., 2016; Mantua et al., 2016; Morin et al., 2008; Nader & Smith, 2003; Nishida & Walker, 2007; Peters et al., 2008; Walker et al., 2002). Specifically, motor skills consolidation is positively associated with greater frequency, density, and number of NREM2 sleep spindles (Barakat et al., 2013; Boutin et al., 2018; Fogel et al., 2007; Fogel & Smith, 2006; Holz et al., 2012; Morin et al., 2008; Nishida & Walker, 2007; Peters et al., 2008). Simultaneous EEG-fMRI recordings further show reactivation of the putamen time-locked to sleep spindles following motor

sequence learning (Fogel et al., 2017). These additional findings suggest that the Dual-Process Hypothesis may be supported in many cases, but it might be an oversimplification of the complex relationship between sleep and memory consolidation.

4.3. Sequential Hypothesis. A complementary perspective for sleep's role in memory consolidation originates from Giuditta's *Sequential Hypothesis*, which emphasises the importance of the cyclical alterations between NREM and REM sleep (Giuditta, 1977, 1985; Giuditta et al., 1995). At the time this hypothesis was proposed, it had been established that NREM sleep was important for restoration and recovery (Giuditta, 2014; Horne & Ostberg, 1977; Shapiro et al., 1981). The Sequential Hypothesis suggests that this restorative phase of NREM sleep, and NREM3 sleep specifically, allows for organizing newly acquired memories (Giuditta, 1985). During the subsequent REM period, these new memories are actively processed and appropriately stored (Giuditta, 1977).

While foundational in terms of the notion that sleep stages sequentially process newly acquired memories, support for this hypothesis has since waned. Nevertheless, REM sleep might still rebalance synaptic weight subcortically (Vyazovskiy et al., 2009), and promote plasticity (Sterpenich et al., 2014). Specifically, REM sleep might selectively strengthen new memories while weakening unnecessary associations (Grosmark et al., 2012; Landmann et al., 2014; Poe et al., 2000; Stickgold et al., 1999). This weakening is thought to occur through the selective pruning of existing, yet unrelated synapses during REM sleep (Li et al., 2017; Poe, 2017). The Sequential Hypothesis introduced a novel way of thinking about the complexities of how sleep sequentially processes memories. Nonetheless, more recent neurobiological evidence suggests that while NREM and REM are indeed complementary, both stages show evidence for consolidation and memory transfer to long-term storage.

4.4. Synaptic Homeostasis Hypothesis. While not a hypothesis about memory consolidation, *per se*, the *Synaptic Homeostasis Hypothesis* (SHY) has important implications for memory consolidation processes that are specific to sleep, and complements other hypotheses of sleep and

memory. The accumulation of slow wave activity with time spent awake, followed by the rapid and exponential dissipation of slow wave activity starting at sleep onset, is proposed to support synaptic homeostasis (Cirelli, 2017; Tononi & Cirelli, 2003, 2006). The SHY states that NREM3 sleep organizes the brain's synaptic and cellular processes to prepare for waking life. Specifically, the SHY is as follows: During wake, we accumulate information that is encoded at the synaptic level, which increases the 'synaptic weight' of a newly formed, or more interconnected set of neurons (Tononi & Cirelli, 2006). During sleep, these accumulated synaptic weights are recalibrated by selectively strengthening certain synapses — while weakening others — thereby restoring synaptic homeostasis while preserving the synapses' relative weights, and consequently the newly encoded information. In this way, new information can be stored, but will not overburden our capacity to process and store new information into long-term storage. The SHY has recently been supported by experimental evidence in line with this reweighting of synapses (De Vivo et al., 2017; Diering et al., 2017; Huber et al., 2013; Kuhn et al., 2016; Lubenov & Siapas, 2008). Overall, SHY suggests that sleep sacrifices alertness of the external world for higher cognitive function; put differently, "*Sleep is the price we have to pay for plasticity*" (Tononi & Cirelli, 2006).

One caveat of this hypothesis, as acknowledged by Tononi & Cirelli (2014), is that the role for REM sleep is less articulated, not only in terms of memory consolidation, but for its role in synaptic homeostasis overall. While the SHY is theoretically based on NREM sleep only, an analogous process might occur in REM sleep – rather than synaptic homeostasis at the cortical level during NREM sleep, subcortical theta power during REM sleep might support REM-related synaptic homeostasis (Tononi & Cirelli, 2014). This has some evidence in rodents, whereby a similar synaptic downscaling process, particularly in the subcortex, is evident at theta power during REM sleep (Vyazovskiy et al., 2009).

4.5. Active Systems Consolidation Hypothesis. Examining the microarchitecture of sleep has provided additional insight into the electrophysiological correlates and putative mechanisms for how

memory is processed during sleep. This body of research gave rise to the *Active Systems Consolidation Hypothesis* (Diekelmann & Born, 2010; Marshall & Born, 2007), which is at present one of the predominant and influential theories on sleep-related memory consolidation. It is complementary with the SHY, but with less emphasis on homeostatic function, and a more narrowed focus on memory consolidation specifically (Diekelmann & Born, 2010). The Active Systems Consolidation Hypothesis suggests that sleep actively strengthens newly acquired memories, as observed through temporal neural signatures (including replay of memories and spindle-slow wave coordination), and through neuroanatomical changes in the brain (*i.e.,* reactivation of the memory trace; Diekelmann & Born, 2010; Klinzing et al., 2019; Rasch & Born, 2013).

Replay is shown to reflect consolidation of hippocampal-dependent memory during offline periods of quiet rest, possibly to transfer new information to the cortex for long-term storage (see section ***3.1 Memory Consolidation and the Hippocampus***). Memory replay in both the hippocampus and the cortex is also apparent during sleep (Dragoi, 2020; Peyrache et al., 2009; Skaggs & McNaughton, 1996; Wilson & McNaughton, 1994). For example, neural activity in the mPFC shows replay of information at the same time as the hippocampus, but only if this sleep period occurs after rule learning (Peyrache et al., 2009).

In addition to replay, sleep spindle-slow wave coupling has been shown to facilitate hippocampal-cortical memory transfer (Diekelmann & Born, 2010; Dudai et al., 2015; Siapas & Wilson, 1998). In humans, the precise timing of spindle-slow wave coupling is a predictor of declarative memory consolidation (Göldi et al., 2019; Helfrich et al., 2018; Muehlroth et al., 2019; Ngo et al., 2013). However, there is little evidence of the role of spindle-slow wave coupling in procedural memory consolidation.

Replay implicitly involves memory trace reactivation, which can be considered the spatial equivalent to temporal replay. The same neuroanatomical regions that are active when learning a task,

can spontaneously reactivate during post-learning sleep, and are time-locked to specific events during sleep. This reactivation is associated with improved procedural performance upon awakening (Bergmann et al., 2012; Boutin et al., 2018; Fogel et al., 2017; Maquet et al., 2000). The first evidence of spontaneous reactivation during sleep observed hippocampal place cells in rats, whereby firing in relation to spatial navigation was reactivated in the same sequential order during post-learning sleep (Pavlides & Winson, 1989). More recent evidence of reactivation comes from studies in humans: Following simple procedural motor sequence learning, the putamen is reactivated and specifically time-locked to sleep spindles (Boutin et al., 2018; Fogel et al., 2017). Overall, sleep has shown to play an active role in the consolidation of both declarative and procedural memory. Evidence for memory replay and memory trace reactivation in the sleeping brain support this process.

5. Focus and Hypotheses of the Present Studies

While sleep actively consolidates both declarative and procedural memory, the focus of this thesis is on procedural memory, specifically procedural memory for cognitive strategies and problem-solving skills. Indeed, the cognitively simple components of procedural memory (*e.g.,* motor skills) are neuroanatomically distinct from their accompanying cognitive strategies and problem-solving skills (see section ***3.4 Procedural Memory for Cognitive Strategies and Problem-Solving Skills***), and it is becoming increasingly clear (Conte & Ficca, 2013; Schmid et al., 2020; C. T. Smith et al., 2004; Walker & Stickgold, 2010) that sleep consolidates procedural memory in a dissociable way, according to the nature of the task demands. Although the neural correlates are known for sleep-related consolidation of procedural memory that involves simple motor skills, less is known about how sleep consolidates procedural memory for strategies and problem-solving skills, which often accompany these simple motor movements.

Behavioural evidence suggests that the benefit from sleep is enhanced as the complexity of the task increases (Blischke & Malangré, 2017; Kuriyama et al., 2004), and that sleep preferentially enhances

memory for the cognitive strategy at the expense of the accompanying motor skills (Conte et al., 2020; van den Berg et al., 2019; Van Hedger et al., 2015). Part of this evidence is supported by work from our group (van den Berg et al., 2019), which demonstrates that **1**) When provided with only the building blocks required to solve a procedural-based problem-solving strategy, the subsequent sleep period might actively process this new information to solve a harder version of the problem — even if they were not originally exposed to this harder version prior to sleep. Importantly, **2**) those who stayed awake throughout the day did not improve on the task. Rather, only when that group was given the opportunity to sleep, did they improve to the same extent as the group that was first given the sleep opportunity. By contrast, the group that had first slept showed no additional improvement when retested a second time, following a period of wake. Finally, **3**) the effect of sleep is specific to the cognitive strategy component of the task, over-and-above the motor skills required to perform the strategy. ***The goal of this thesis is to expand on the behavioural evidence to identify, through neuroimaging methods, how the sleeping brain consolidates procedural memory for cognitive strategies and problem-solving skills.***

5.1. Study One: REM Sleep and Consolidation of Procedural Memory for Cognitive Strategies and Problem-solving Skills. Increases in REM sleep duration and eye movement density are associated with improvements on motor skills that include cognitive strategies and problem-solving skills (Brand et al., 2010; Buchegger & Meier-Koll, 1988; Fogel et al., 2015; Mandai et al., 1989; Nielsen et al., 2015; C. T. Smith et al., 2004; C. T. Smith & Weeden, 1990). However, it is unlikely that the eye movements *per se* are directly responsible for sleep-related memory consolidation, especially considering they are generated by the PGO circuitry, which has little to do with memory systems. More recent methodological advancements (*e.g.*, automated eye movement detection and event-related spectral perturbation [ERSP] analyses) have elucidated how rapid eye movements might be a marker for concomitant neural activity. For example, whereas rapid eye movements during REM sleep have long been associated with mastery of learning a second language (De Koninck et al., 1989; Hébert et al., 1992;

Hébert & De Koninck, 1993), recent methodological advancements extended these findings to show that theta power time-locked to these rapid eye movements not only increase as language learning progress, but the extent of the increase in theta power is correlated with mastery of the new language (Thompson et al., 2021). It is therefore likely that a similar time-locking of theta to rapid eye movements during REM sleep is associated with consolidation of procedural memory for cognitive strategies and problem-solving skills.

In addition, little evidence is available on the distinction between phasic REM sleep and tonic REM sleep in terms of memory consolidation. Most research has focused on eye movements themselves in REM sleep. For example, increased density of phasic eye movements during REM sleep are associated with improved performance (Peters et al., 2007; C. T. Smith et al., 2004). Even among the available evidence on phasic and tonic states for memory consolidation, there are mixed findings: Introducing a cue while learning a cognitive strategy (C. T. Smith & Weeden, 1990) or motor sequence (Guerrien et al., 1989), then reintroducing the same cue during REM sleep, shows benefits to improvement only if the cue is reintroduced during the phasic state, thus implicating phasic REM sleep in memory consolidation. By contrast, others have shown that tonic REM sleep duration is positively associated with learning a complex gross-motor skill (*i.e.,* inverse bicycle riding; Bothe et al., 2019). The distinction between phasic and tonic REM states in its role for memory consolidation therefore requires further research.

The purpose of this first study was to explore whether and how phasic and tonic REM states are associated with consolidation of procedural memory that requires cognitive strategies used for problem-solving skills. **It was hypothesized that 1**) improvement on the ToH would benefit more from a retention period of sleep as compared to a period of daytime wakefulness, thus reflecting a benefit of sleep for memory consolidation; **2**) learning-dependent increases in theta power time-locked to EMs during REM sleep will be observed, **3**) increased EEG theta power time-locked to EMs during phasic REM sleep will

be distinct from tonic REM sleep, and, **4**) sleep-dependent behavioural improvements will be associated with EEG theta power time-locked to EMs during phasic REM sleep.

5.2. Study Two: Neural Correlates of Sleep-Related Consolidation for Cognitive Strategies and Problem-solving Skills. During initial learning of a novel sequence of motor movements, the hippocampus, putamen, parietal cortex, and premotor cortices are activated (Albouy et al., 2008; Gheysen et al., 2010; Grafton et al., 1994; Schendan et al., 2003; Tzvi et al., 2014; Ungerleider et al., 2002), and this activation is associated with sleep-related improvement on motor sequence learning (Albouy, Fogel et al., 2013; Boutin et al., 2018; Debas et al., 2010; Debas et al., 2014; Fogel et al., 2017). Specifically, the hippocampus and striatum interact during motor sequence learning (Albouy et al., 2016; Albouy, Fogel, et al., 2013; Albouy, King, et al., 2013; Poldrack & Rodriguez, 2003). As memory consolidation takes place over several days, recruitment of the ventro-lateral putamen increases with time (Lehéricy et al., 2005). The caudate also becomes increasingly activated with improvement, while parietal cortices show decreased activation (Albouy et al., 2012). This suggests that the hippocampal-striatal-cortical relationship weakens as learning becomes increasingly automatic, whereby the hippocampus and parietal cortex become less involved over time, and the striatum becomes more involved over time (Albouy et al., 2012).

The sleep-related neural correlates have been well-examined for the consolidation of simple motor skills, but this remains to be investigated when these skills require the acquisition of a novel cognitive strategy. Whereas the putamen is involved in simple procedural motor learning, activation of the caudate is specifically when executing skills requiring cognitive strategies and problem-solving skills (see section ***3.4.1. Neural Substrates of Cognitive Strategies and Problem-Solving Skills***). Accordingly, sleep might preferentially consolidate memory for the cognitive strategy via the caudate — rather than the simple procedural putamen-related component (Debas et al., 2010; Debas et al., 2014; Fogel et al., 2017) — among other areas, including the PFC and hippocampus.

The purpose of this third study is to examine the sleep-related neuroanatomical substrates of procedural memory involving cognitive strategies required for problem solving. **It was hypothesized that 1**) sleep will benefit the consolidation of problem-solving skills, and that **2**) sleep will preferentially transform and enhance brain regions recruited during acquisition. More specifically, we predicted that activation in regions related to problem solving (*i.e.,* the caudate, hippocampus, and prefrontal cortex) would be enhanced following sleep *vs.* an equivalent period of wake. Areas associated with the task's simple motor component (*i.e.,* putamen), will show no benefit from sleep *vs*. wake.

5.3. Study Three: The Role of Sleep for Functional Communication Between Brain Regions Implicated in Cognitive Strategies and Problem-solving Skills. Functional communication between brain regions is necessary for the transfer of information from subcortical to cortical areas during memory consolidation. A relatively new approach to understanding how brain regions communicate with one another is the use of functional connectivity approaches with fMRI data (Biswal et al., 1995). Functional connectivity typically measures the correlation between temporal time-series of brain states. These data are normally acquired during a period of quiet rest (hence called 'resting state' functional connectivity analysis). It was first observed by Biswal (1995), who showed that the temporal time series between the left and right motor cortex — despite being structurally distinct — are simultaneously engaged during a simple motor act of squeezing a ball.

This approach has only recently been applied to the field of sleep. It has been demonstrated that the degree of left and right motor cortex functional connectivity immediately following learning a simple motor task, predicts the benefit of sleep to overnight improvement the next morning (Gregory et al., 2015). In addition, increased functional connectivity between the caudate and the hippocampus was observed following a period of sleep, when auditory cues of motor sequences were reintroduced during the sleep-related consolidation period (Cousins et al., 2016). Recently, simultaneous EEG-fMRI recordings were used to investigate resting-state functional connectivity during initial learning of simple

motor sequences, and subsequently during post-training sleep (Vahdat et al., 2017). The same structures recruited during learning (*i.e.,* putamen, hippocampus, motor cortex) were not only reactivated during sleep, but the extent of the strengthened functional connectivity of the putamen was directly associated with overnight behavioural improvement. Overall, research into functional connectivity related to sleep and memory consolidation is scarce. Nevertheless, this approach can provide valuable insight into how sleep strengthens the communication between brain areas involved in memory consolidation.

The neuroanatomical areas within the hippocampal-striatal-cortical network that showed sleep-related neural activation from *Study 2*, were used as Regions of Interest (ROIs) for functional connectivity analysis in *Study 3*. In this way, the purpose of this third study was to identify how these areas communicate before and after an offline consolidation period sleep, thus elucidating the temporal transformation of sleep-dependent consolidation of procedural memory for novel cognitive strategies and problem-solving skills. **It was hypothesized that: 1**) functional communication between the hippocampus, striatum (*i.e*., caudate, putamen), motor cortex, and prefrontal cortex (*i.e*., OFC and dlPFC) would increase after acquiring a novel cognitive procedural strategy; **2**) these changes in functional connectivity would be most evident following an offline consolidation period of nocturnal sleep compared with a day of wakefulness; and **3**) the changes in functional connectivity following a period of sleep would be correlated with overnight improvement on the execution of cognitive strategies and problem-solving skills.

Additional Readings

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Chapter 2: Study 1

Eye movements during phasic vs. tonic REM sleep are biomarkers of dissociable EEG processes for the consolidation of novel problem-solving skills

Abstract

The hallmark eye movement (EM) bursts that occur during Rapid Eye Movement (REM) sleep are markers of consolidation for procedural memory involving novel cognitive strategies and problem-solving skills. Examination of the brain activity associated with EMs during REM sleep might elucidate the processes involved in memory consolidation, and may uncover the functional significance of REM sleep and EMs themselves. Participants performed a REM-dependent, novel procedural problem-solving task (*i.e.,* the Tower of Hanoi; ToH) before and after intervals of either overnight sleep (*n*=20) or a daytime 8-hour wake period (*n*=20). In addition, event-related spectral perturbation (ERSP) of the electroencephalogram (EEG) time-locked to EMs occurring either in bursts (*i.e*., phasic REM), or in isolation (*i.e.,* tonic REM), were compared to sleep on a non-learning control night. ToH improvement was greater following sleep compared to wakefulness. During sleep, prefrontal theta (~2-8 Hz) and central-parietal-occipital sensorimotor rhythm (SMR) activity (~8-16 Hz) time-locked to Ems, were greater on the ToH night versus control night, and during phasic REM sleep, were both positively correlated with overnight memory improvements. Furthermore, SMR power during tonic REM increased significantly from the control night to ToH night, but was relatively stable from night to night during phasic REM. These results suggest that EMs are markers of learning-related increases in theta and SMR during phasic and tonic REM sleep. Phasic and tonic REM sleep may be functionally distinct in terms of their contribution to procedural memory consolidation.

Keywords: sleep, memory consolidation, procedural memory, problem solving, phasic REM sleep, tonic REM sleep, theta, sensorimotor rhythm

1. Introduction

A consolidation period of sleep (as compared to wakefulness) after learning new procedural skills, and in particular, skills that require the acquisition of *new rules and cognitive strategies,* results in performance boosts in speed, accuracy, and insight (Brand et al., 2010; Conte et al., 2020; Durrant et al., 2011; Fogel & Smith, 2006; Lewicki et al., 1987; Lewis et al., 2018; Nielsen et al., 2015; Smith & Weeden, 1990; van den Berg et al., 2019; Wagner et al., 2004). This post-learning period of sleep is marked by changes to sleep architecture (*e.g*., rapid eye movement [REM] sleep duration; Barsky et al., 2015; Brand et al., 2010; Schredl & Erlacher, 2007; Smith et al., 1974; Smith & Butler, 1982; Stickgold et al., 2000; and increased rapid eye movements (EMs) during REM sleep; Buchegger et al., 1991; Buchegger & Meier-Koll, 1988; De Koninck et al., 1989; De Koninck & Prévost, 1991; Mandai et al., 1989; Maquet et al., 2000; Nielsen et al., 2015; Peigneux et al., 2003; Peters et al., 2007; Smith et al., 2004, 2004; Smith & Lapp, 1991; Smith & Weeden, 1990). These changes are thought to reflect sleep-specific memory consolidation via memory trace reactivation and replay (Klinzing et al., 2019), resulting in the transformation/strengthening of the newly formed memory trace (*e.g*., increased activation/recruitment of task-specific brain areas [van den Berg et al., 2021] and strengthened functional connectivity [van den Berg et al., 2023]).

If REM sleep does not occur, or if it is reduced or disrupted during this critical window of time, memory consolidation for cognitively complex procedural memory is impaired as compared to normal sleep (Bjorness et al., 2005; Conway & Smith, 1994; Plihal & Born, 1997; Sandys-Wunsch & Smith, 1991; Smith & Smith, 2003). This deficit is not observed following non-REM sleep disruption (Djonlagic et al., 2020; Laventure et al., 2016; Mednick et al., 2013; Smith et al., 1998; Watts et al., 2012). REM sleep is thus necessary for optimal consolidation of procedural skills that involve the acquisition of new rules and novel cognitive strategies required for problem solving. The polysomnographic (PSG) features of REM sleep (*i.e.,* eye movements themselves) are markers of memory improvements, and further

investigation of their neural correlates may provide insight into the processes and mechanisms that involve the consolidation of novel cognitive strategies necessary for problem-solving skills.

Rapid EMs during REM sleep are generated by the ponto-geniculo-occipital (PGO) circuity (Callaway et al., 1987; Datta & Hobson, 1994; Gott et al., 2017; Mouret et al., 1963). Although PGO waves are not easily measured in humans, studies using invasive recording techniques have identified EM-related PGO activity in patients with epilepsy (Frauscher et al., 2018), and in patients with Parkinson's Disease (Fernández-Mendoza et al., 2009). Non-invasive techniques such as simultaneous EEG and functional magnetic resonance imaging (fMRI) have also demonstrated increased recruitment of the thalamus and occipital cortex when time-locked to rapid EMs during REM sleep (Miyauchi et al., 2009; Wehrle et al., 2005). However, the pons, geniculate nucleus of the thalamus and primary visual cortex are not strong candidates for the consolidation of cognitively complex memory. The movement of the eyes and the PGO circuitry themselves are therefore unlikely to be directly involved in memory consolidation. Rather, we hypothesize that rapid EMs are a marker of concomitant neocortical processing of newly acquired memory traces.

It has been proposed that the human correlate of PGO waves is REM sleep theta (Frauscher et al., 2018), and importantly, the human analog to rodent theta (~4-8Hz) has a broader frequency range that includes slower frequencies in the 2-8 Hz range (Bódizs et al., 2001; Clemens et al., 2009; 2013; Frauscher et al., 2020; Moroni et al., 2007; Sato et al., 1997). There is evidence that enhanced theta rhythms occur during EM-rich (*i.e.*, phasic) REM sleep (Grosmark et al., 2012; Montgomery et al., 2008; Simor et al., 2016), and it has been proposed that this may reflect memory processing (Boyce et al., 2016; Durrant et al., 2015; Fogel et al., 2009; Jones & Wilson, 2005; Poe et al., 2000; Swift et al., 2018). In rodents, REM sleep theta (~4-8 Hz) originates from hippocampal rhythmic slow activity and hippocampal-neocortical coordination (Montgomery et al., 2008), which is associated with memory consolidation (de Almeida-Filho et al., 2021). In addition, inducing theta during REM sleep improves

memory for maze navigation (Boyce et al., 2016), thus suggesting that theta activity during REM sleep has a causal effect on memory consolidation. In humans, REM sleep theta power in the ~4-8 Hz range has been associated with processing schema-conformant memories (Durrant et al., 2015). Moreover, our group has employed a novel event-related spectral perturbation (ERSP) approach, revealing that ~4-8Hz theta power time-locked to EMs is associated with procedural aspects of learning a second language (Thompson et al., 2021). Previously, in these same data, De Koninck et al., observed increased REM duration and improved proficiency in the new language occurring at the onset of dreaming in the newly-learned second language (De Koninck et al., 1989; Hébert & De Koninck, 1993, 1994). It is therefore likely that cortical theta rhythms are associated with EMs during REM sleep. One of the main aims of the current study is to examine which learning-related changes in EEG frequencies (*e.g.*, theta) are time-locked to rapid EMs using this novel ERSP approach. This may reveal the brain oscillations that are time-locked to EMs, which are associated with REM-related memory consolidation for problem-solving skills.

Importantly, REM sleep is not a homogeneous sleep stage. It can be subdivided into two distinct states: "*phasic*" and "*tonic*" REM sleep. Phasic REM sleep is defined by the presence of bursts, or trains of EMs, whereas tonic REM sleep is characterized by the relative absence of EMs, or isolated EMs. The focus of previous research has been on phasic REM sleep. Relatively little is known about the distinct functional significance of phasic and tonic REM sleep, when directly compared. Two of the first studies to directly investigate this in humans employed targeted memory reactivation following Morse Code learning (Mandai et al., 1989) and following cognitive strategy learning (Smith & Weeden, 1990). Targeted memory reactivation involves re-introducing a cue which was first acquired during learning, during the subsequent sleep period, for the aim of enhancing the offline sleep-related consolidation process by cued 'reactivation' of the newly acquired memory. In both cases, enhanced memory consolidation was observed only if the cue was delivered when precisely timed to EMs, but not when

delivered during REM sleep in the absence of EMs. In addition, Bothe et al. (2019) have shown that performance improvements for dissociable aspects (*e.g*., accuracy) of a gross-motor procedural skill (*i.e*., inverse bicycle steering) were associated with increased tonic REM sleep duration. Thus, tonic REM sleep might also be important for memory processing, but this possibility has been largely unexplored.

Together, these studies suggest that phasic and tonic REM sleep might be differentially involved in the consolidation of procedural memories, and in particular, for novel cognitive strategies required for problem-solving skills. However, the paucity of research in humans warrants further investigation. Here, we tested participants on a procedural task (the Tower of Hanoi; ToH) which requires the acquisition of a novel cognitive strategy to solve the problem. Participants performed this task before and after either a night of sleep, or a day of wakefulness. We then compared the characteristics of the sleep group's REM sleep microarchitecture (*i.e*., phasic REM sleep marked by EM bursts, and tonic REM sleep marked by isolated EMs, or, the absence of EM bursts,) to a control night — during which no learning occurred — to investigate the learning-dependent changes in REM sleep EEG characteristics involved in memory consolidation for novel problem-solving skills.

We hypothesized that: **1)** improvement on the ToH would benefit more from a retention period of sleep as compared to a period of daytime wakefulness, thus reflecting a benefit of sleep for memory consolidation; **2)** learning-dependent increases in EEG spectral power (*e.g*., theta power) time-locked to EMs during REM sleep will be observed (ToH night *vs*. control night); **3)** increased EEG spectral power time-locked to EMs during phasic REM sleep will differ from tonic REM sleep, and; **4)** this increase in theta power time-locked to phasic REM sleep will be associated with sleep-dependent behavioural improvements.

2. Methods

2.1. Participants. Power analysis determined that a sample size of $n > 18$ would be needed to detect a medium effect size ($d = 0.6$) for ERSP analyses, and $n > 14$ for behavioural effects ($\alpha = 0.05$

with power set to 80%). Participants were recruited via poster advertisements at the University and nearby surrounding areas, through social media and by word-of-mouth. We collected $n = 20$ per group for a total target study size of $n = 40$. Participants (between 20 and 35 years of age) were excluded if they were left-handed, a shift worker, took medications known to interfere with sleep, had an irregular sleep schedule (*i.e.*, bedtime outside of 22:00 and 01:00, or wake time after 09:00), a body mass index (BMI) > 30, hand/finger mobility problems, if they had taken a trans-meridian trip in the previous month, or if they consumed excessive nicotine (*i.e.*, considered themselves a "*non-smoker*"), caffeine (*i.e.*, consumed < 2 drinks/day) or alcohol (*i.e.*, consumed < 7 drinks/week). Participants were also excluded if they considered themself a poor sleeper, had a history of chronic pain, seizures, or head injury, or had experience with the ToH (or similar) task. To be included, participants had to score < 10 on the Beck Anxiety (Beck et al., 1988) and Beck Depression Inventories (Beck & Beamesderfer, 1974), and have no signs of sleep disorders indicated by the Sleep Disorders Questionnaire (Douglass et al., 1994).

Participants who met initial screening criteria underwent a PSG sleep disorder screening and acclimatization night, approximately one-week before the subsequent sessions. Based on the results of the PSG screening night, participants were excluded from the study if their sleep efficiency was < 80 %, if they had > 5 respiratory events/hour (indicating signs of sleep apnea), or indications of parasomnias during sleep. All participants were asked to wear a Motionlogger actigraph (a wrist-worn accelerometer; Ambulatory Monitoring Inc., Ardsley, NY, U.S.A.) and to complete a log of their sleep/wake habits for the duration of the study to ensure compliance with the experimental protocol.

The final sample comprised 40 healthy young adults (23 females; aged 20 and 35 years; M_{AGE} = 25.05, SD = 4.45). Participants were randomly assigned to either the sleep (Sleep; $n = 20$; 11 females; M_{AGE} = 25.45, SD = 5.36) or wake (Wake; $n = 20$; 12 females; M_{AGE} = 24.65 SD = 4.49) group.

2.2 Ethics Statement. All study procedures were approved by the Research Ethics Boards at the University of Ottawa and The Royal's Institute of Mental Health Research (IMHR). All participants

provided written informed consent prior to participation and were financially compensated for their participation.

2.3. Experimental Protocol. Following the PSG screening night, eligible participants returned to the lab on two occasions: once for the ToH session, and once for a control session (see **Figure 1** for the study design). The order of the ToH and control sessions was counterbalanced across participants. Upon arrival to the lab, participants completed the training session, which involved performing 8 trials of the ToH (or control task; see below). This was followed by either an 8-hour overnight PSG recording (sleep group), or an 8-hour daytime wake period (wake group). Following these intervals, and after a > 30-minute wake period to allow the effects of sleep inertia to dissipate in the Sleep group, all participants completed the retest session, comprising 4 trials of the ToH (or control task; see below). The control session protocol was identical to the ToH session, except participants instead performed a control task (see ***Tower of Hanoi Control Task***, below), during which no learning occurred.

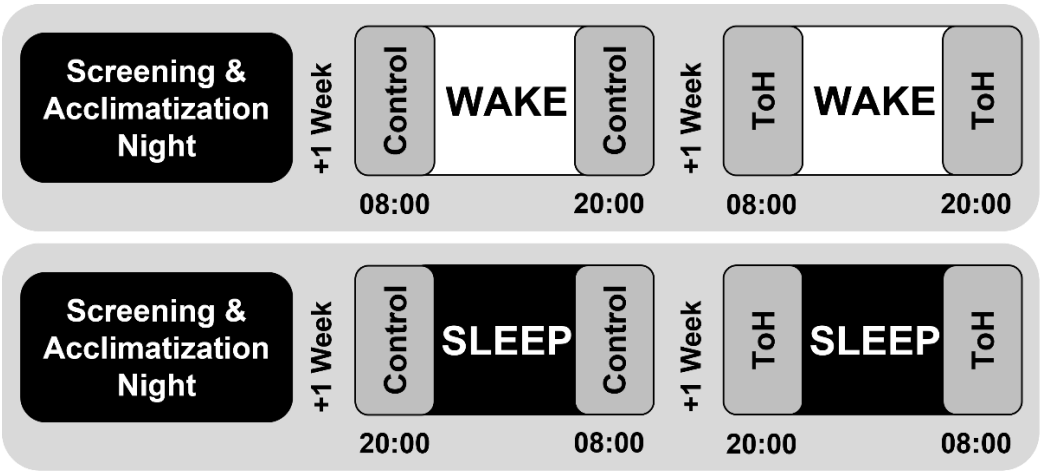

Figure 1. Study Design. Participants in the Sleep and Wake groups first underwent an overnight screening & acclimatization night. One week following the screening & acclimatization night, participants in the Sleep group were trained on the ToH for 8 trials at 20:00. After, they underwent an 8-hour overnight PSG-recorded sleep opportunity. Upon awakening, and after allowing a > 30 minute wake period to allow the effects of sleep inertia to dissipate, they were retested on the 4 trials of the ToH. Participants in the Wake group were trained on the ToH for 8 trials at 0800, then stayed awake for the remainder of the day (confirmed via Actigraphy). At 20:00, these participants were retested on 4 trials of the ToH. Importantly, the time interval between Training and Retest for conditions was constant for both groups. A counterbalanced control session was also performed for each group, whereby the same protocols were followed, except participants were trained and retested on the control task. Although visually identical to the ToH, this control task provided no opportunity to learn the cognitive strategy by prompting random button presses.

2.4. Behavioural Tasks and Analysis

2.4.1 Tower of Hanoi. A 5-disk version of the ToH was coded in MATLAB R2016a (Mathworks Inc., Natick, MA, USA) using the Psychophysics Toolbox extension v3.0.12 (Brainard, 1997; Kleiner et al., 2007) for Windows (Microsoft, Redmond, WA, USA). The initial appearance of the task includes three identical, equally-spaced pegs, with 5-disks stacked on the far-left peg in ascending order of size (*i.e.*, largest disk on the bottom, smallest disk on the top). Participants were instructed that, for each trial, the objective of the task was to transfer all disks from the initial position on the far-left peg to the final position on the far-right peg in the same ascending order. This was to be accomplished while obeying three constraints: **1)** only one disk can be moved at a time, **2)** only the upper-most disk from any one of the three pegs can be moved, and, **3)** a disk can only be moved to an empty peg, or on top of another disk that is larger in size. Participants were also told to perform the task "*as quickly and as accurately as possible*". Participants could control the on-screen movement of the disks with a button pad (model HHSC-2x4-C; Current Designs Inc., Philadelphia PA, USA), by pressing one of three push buttons equally spaced apart in a horizontal row. Participants controlled the disks via the button pad using their right index, middle, and ring fingers corresponding to the first (*i.e.*, far-left peg), second (*i.e*., middle peg) and third (*i.e*., far-right peg) buttons, respectively. The buttons controlled the movement of the disks '*from*' (feedback for this movement was indicated by a green dot above the corresponding peg) and '*to*' (feedback for this movement was indicated by a red dot about the corresponding peg) one of the three pegs. In the case of an incorrect button press/illegal move, green or red dots did not appear. A trial ended when all five disks were stacked in ascending order on the far-right peg, or if the maximum number of moves was reached before successful completion of the task. The maximum number of moves for the 5-disk task was set at 93 (*i.e.*, three times the optimal number of moves $[2^N - 1]$, where N is the number of disks, *i.e*., $2^5 - 1 = 31$).

The variables of interest for the ToH task were speed (*i.e.*, time to complete each ToH trial) and accuracy (Mean Absolute Percentage Error; MAPE). The MAPE can be interpreted as a percentage of perfect performance (*e.g.*, 100% reflects perfect performance, whereas 50% reflects making twice as many errors as perfect performance, and 0% represents an infinite number of moves). The % improvement for all variables was calculated by taking the performance in the first retest trial minus performance in the last training trial, divided by performance in the last training trial multiplied by 100. All behavioural statistical analyses were carried out using SPSS Statistics version 25 (IBM, Armonk, New York, U.S.). Independent samples *t*-tests compared sleep and wake groups on measures of speed and accuracy.

2.4.2 Tower of Hanoi Control Task. Participants performed the control task during the control sessions. The control task was visually identical to the ToH task and adhered to the constraints of the ToH, however, participants were guided on random movements of disks *from* (visually indicated by a green dot above the peg) and *to* (visually indicated by a red dot above the peg) one of the three pegs. Each trial of the control task ended when a total of 31 randomly guided moves were completed, corresponding to the minimum number of moves it takes to perfectly complete the 5-disk ToH task. Participants performed four trials of the control task.

2.5. PSG Recording and Analysis

2.5.1 Recording Parameters. PSG was recorded with the Embla N7000 32-channel amplifier system (Natus, Pleasonton, CA, USA) sampled at 500 Hz. The EEG (Fp1, Fpz, Fp2, F3, Fz, F4, C3, Cz, C4, P3, Pz, P4 and Oz), mastoid derivations (M1 and M2), and left and right electrooculogram (EOG) were referenced to Fpz online, and placed according to the international 10-20 system (Jasper, 1958). A submental electromyogram (EMG) channel was recorded as a bipolar derivation.

2.5.2. Preprocessing. Preprocessing of the PSG was carried out using functions from the EEGLAB toolbox (Delorme & Makeig, 2004) for MATLAB (Mathworks Inc., Natick, MA, USA).

Participants' EEG and EOG channels were re-referenced offline to an average of the mastoid channels (M1 and M2), and bandpass filters were applied as follows: EEG channels (0.3–35 Hz), EOG channels (0.3–10 Hz), and the EMG channel (10–50 Hz). Movement artifacts were automatically detected using a custom script created for EEGLAB with an amplitude threshold cutoff of 25 μV from the first derivative of the EMG signal with a minimum duration of 1 second. The resulting artifact markers were then visually supervised for false negatives and false positives by an expert scorer using the "*Mark Events*" plugin for EEGLAB (https://github.com/stuartfogel/MarkEvents).

2.5.3 Analysis. Manual sleep stage scoring was completed using RemLogic analysis software (Natus, San Carlos, CA, USA) and by an expert polysomnographic technologist according to standard criteria (Iber et al., 2007; Rechtschaffen & Kales, 1968). The macro-sleep architecture variables of interest obtained from the PSG recordings included the total sleep time (TST; calculated as the total time spent asleep between "*lights off*" and "*lights on*") and the time in minutes spent in Stage 1 (NREM1) sleep, Stage 2 (NREM2) sleep, Stage 3 (NREM3) sleep, and rapid eye movement (REM) sleep.

2.5.4. Rapid Eye Movement Event Detection. EMs were detected using an adapted version of previously validated approaches using a matched filtering algorithm (Hatzilabrou et al., 1994; Yetton et al., 2016), most recently employed by our group (Thompson et al., 2021). Compared with other validated algorithms, this approach was found to be the single-best performer in terms of reliability and has the most balanced recall and precision (Yetton et al., 2016). This matched filtering algorithm is adapted from Yetton et al.'s (2016) version of Hatzilabrou et al.'s (1994) original detection method, which was widely available in Stellate Harmonie (Stellate Systems, Montreal, Canada), and can be freely accessed online (https://osf.io/fd837). EOG signals from REM sleep were first filtered from 0.5–10 Hz and smoothed using a Hamming window. The filtered EOG signals were divided into consecutive 1 second windows. As per Yetton et al.'s (2016) validated approach, the window size was determined to be large enough to include a complete REM movement. Other window sizes (*e.g.*, 0.5, 0.7, 1.2, 1.4, 1.6 sec) were not found

to improve performance. EMs were then identified by their correlation using the magnitude of the squared correlation with a template available in Yetton et al. (2016) of a typical EM for the left and right EOG signals (optimal correlation p = 0.0005). Only monocular eye movements above the amplitude threshold of 23μV were included in this detection step. Finally, only conjugate EM events, *e.g.*, left and right monocular eye movements occurring in the same time window, were then marked on the original EOG trace at the peak (maximum) amplitude of the EM (**Figure 2**).

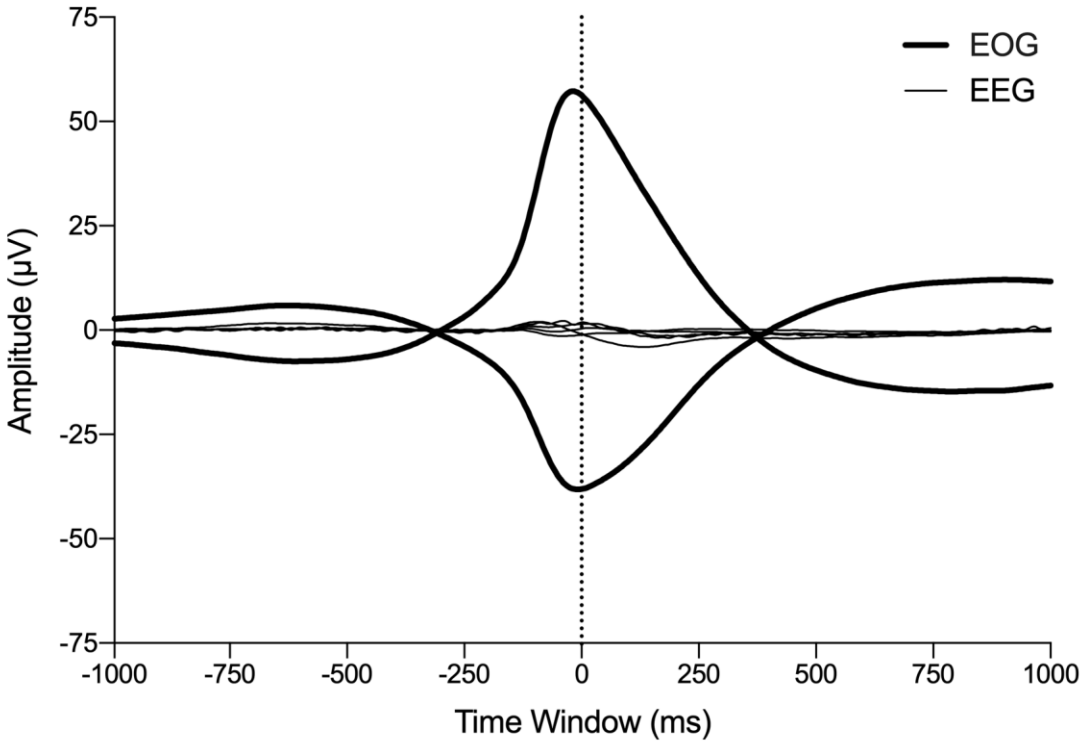

Figure 2. ERP plots. Timing and duration of average peak EMs (LEOG and REOG) and midline EEG channels (Fpz, Fz, Cz, Pz, Oz) during REM sleep, relative to the peak EM (time = 0ms, +/- 1000ms). Activity in left and right EOG channels shown for positive and negative deflections. Deflections in the amplitude of EEG channels time-locked to EMs that could be considered artifactual were negligible (<5μV) and occurred below 2 Hz. No discernable deflections are observed on the EEG channels from about | 250 | < | 1000 | ms.

2.5.5. REM Burst Detection. A Markov chain statistical burst detection analysis was used to objectively identify and characterize phasic REM sleep (*i.e.*, periods when EMs are in a burst) and tonic REM sleep (*i.e.,* periods when bursts of EMs do not occur, or EMs occur in isolation). This method employed the *'pybursts'* library for Python (https://pypi.org/project/pybursts), adapted to take event

onsets as input from EEGLAB datasets. The algorithm can model bursts of any event in a time series (*e.g.*, EM event onsets). The method is based on Kleinberg's burst detection algorithm (described in '*Bursty and Hierarchical Structure in Streams*'; Kleinberg, 2003), and uses an infinite hidden Markov model to detect periods of increased activity in a series of discrete events with known times. The model is a hidden Markov process in which, after each event, the state of the system probabilistically determines how much time will pass until the next event occurs. This approach allows for the temporal hierarchical structure to be extracted, indicated by higher burst intensity levels ("*burst states*" *i.e.*, that define phasic REM sleep). EMs that were not identified as being part of a burst of EMs were considered "*isolated*" and occurring during tonic REM sleep. **Figure 3** illustrates a sample hypnogram (**Figure 3A**), the corresponding detection of EMs during REM sleep (**Figure 3B**), and the hierarchical structure of bursts of EMs (**Figure 3C**). Burst event measures of interest included: burst duration, burst height (the number of nested levels in the burst hierarchy), sub-bursts (the number of nested bursts), burst density (sub bursts/burst height) and number of EM events in a burst.

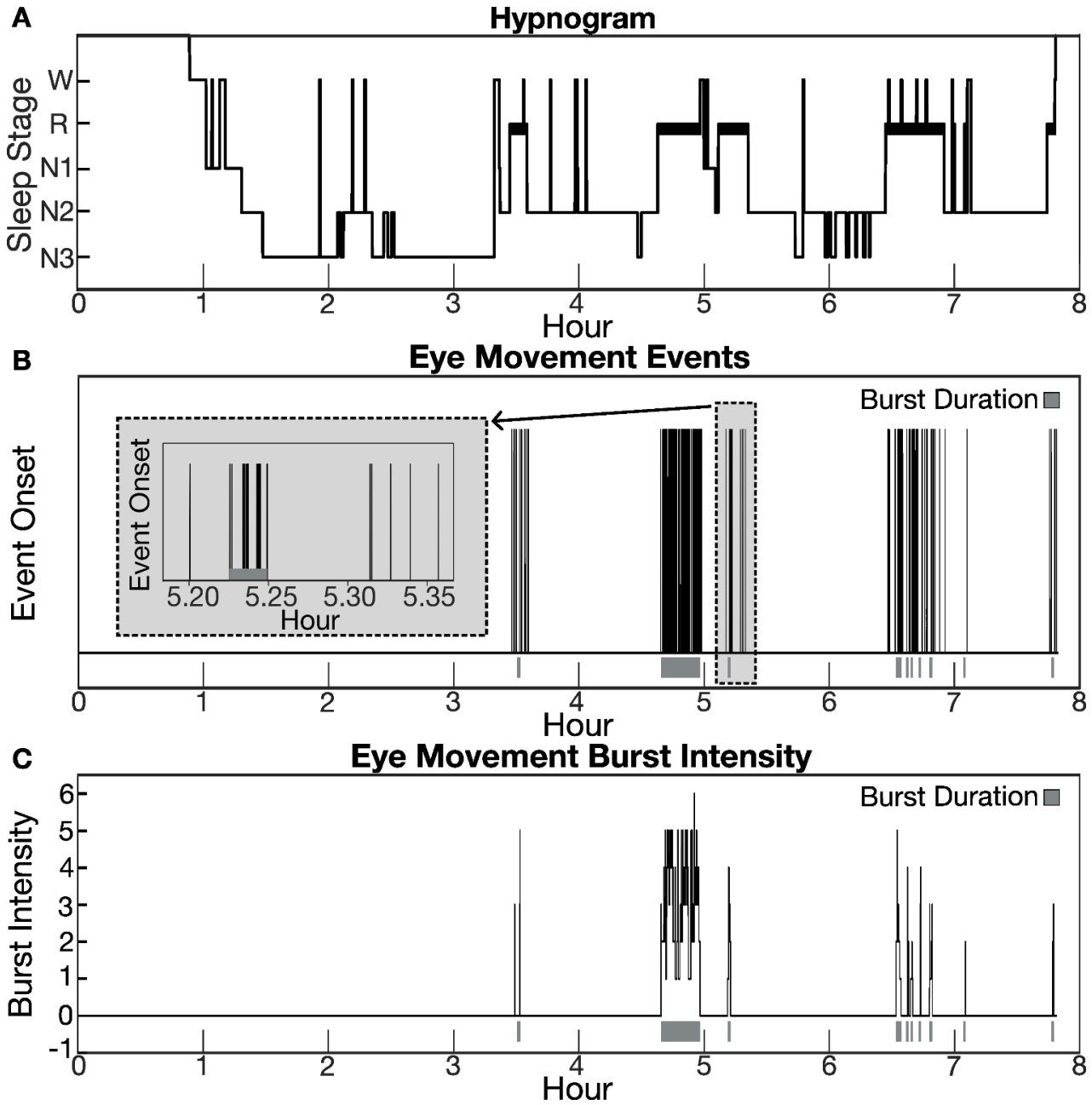

Figure 3. Sample EM detection. A: Sample of a single participant's hypnogram, **B:** detected EM events; inset panel shows EM events at a higher time resolution, and, **C:** intensity of EM bursts. Burst Duration is indicated in panels **B** and **C** by grey bars above the X-axis, indicating periods of phasic REM sleep. Detected EM events without grey bars (see example in **B** inset) are considered isolated EMs, occurring during tonic REM sleep.

2.5.6. ERSP Analysis. Each participant's preprocessed, artifact detected, sleep scored and EM event-detected recordings were subsequently analyzed using an ERSP approach, available in EEGLAB (Delorme & Makeig, 2004). ERSP analyses of the EEG were performed using EMs as the events of

interest. ERSP analyses of the EEG were performed using individual EMs peak latencies as the events of interest. Given that we did not have any *a priori* hypotheses about lateralization effects, changes in power in the EEG were examined at five individual scalp locations along the midline (i.e., Fpz, Fz, Cz, Pz, Oz). Data were segmented into 3-second epochs (i.e., −1500 to 1500 ms) centred around each individual EM peak latency. This was done for both eye movement events occurring during phasic REM sleep and for eye movement events occurring during tonic REM sleep. This ERSP approach extends previous work from our group (Thompson et al., 2021), to investigate event-related changes in EEG power time-locked to EMs during REM sleep, and their role in memory consolidation.

Time-frequency decomposition of the data segments was performed using Morlet wavelet convolution implemented in EEGLAB's "*newtimef.m*" function (Delorme & Makeig, 2004; Grandchamp & Delorme, 2011). Wavelets ranged in frequency from 2 Hz to 17 Hz in 150 linearly spaced steps (0.10 Hz), and in length from 3 cycles at the lowest frequency to 8.5 cycles at the highest frequency. Wavelets were applied across a time range of -1500 ms to 1500 ms in 300 linearly spaced steps (10 ms). Spectral power for each condition was baseline corrected using the average power at each frequency between -1500 ms and -1000 ms.

To identify power differences between nights, a permutation-based cluster analysis, implemented in EEGLAB (Delorme & Makeig, 2004) was then conducted on the power values of all time/frequency points obtained from the wavelet decomposition. The cluster analysis, implemented in EEGLAB, employs t-tests to identify statistically significant time-frequency clusters. Once these clusters were identified, we took the additional step to apply Monte Carlo permutation-based correction for multiple comparisons and employed Wilcoxon tests (Wilcoxon, 1946) for the raw power values in each significant cluster to test our hypotheses (see EEGLAB documentation for "statcondfieldtrip" for more information), as the output from the preceding step are often not normally distributed (Grandchamp & Delorme, 2011). These analyses tested for differences in power between the ToH and non-learning control nights, for

EMs occurring either in bursts (*i.e*., phasic REM sleep), or in isolation (*i.e*., tonic REM sleep). Significant effects were further corrected at the cluster level for multiple comparisons using the Holm-Bonferroni method (Holm, 1979).

2.5.7. Eye Movement Bursts vs. Isolated Eye Movements Direct Comparisons. Next, we analyzed EEG power from the above significant clusters for follow-up analyses, by first drawing 0.5 Hz by 50 ms diameter spheres around the peak of the significantly different cluster observed between ToH and control nights, and then extracting those spheres for each participant at the individual level. These values were extracted to directly compare power time-locked to EMs in bursts *vs*. isolated EMs, across ToH and control nights. Accordingly, Session (ToH night, control night) by EM type (Bursts, Isolated) 2 x 2 ANOVAs were performed on these extracted spheres (*i.e.,* power differences as the dependent variable), followed by simple effects *t*-tests, where appropriate.

2.5.8. Brain-Behaviour Correlations Analysis. The same EEG power values extracted around the peak of significant clusters described above were used to follow-up if EEG power changes from ToH to control nights were associated with overnight improvement on the ToH. Power differences were computed as percent change from the control night to the ToH night for power values time-locked to EMs in phasic or tonic REM sleep.

3. Results

3.1. Behavioural Improvement. Independent samples t-tests demonstrated that the sleep group improved performance over the consolidation interval as compared to the wake group in terms of both speed ($t(38) = 6.69$, $p < 0.0001$, $d = 2.12$) and accuracy ($t(38) = 2.08$, $p = 0.044$, $d = 0.66$; **See Figure 4**).

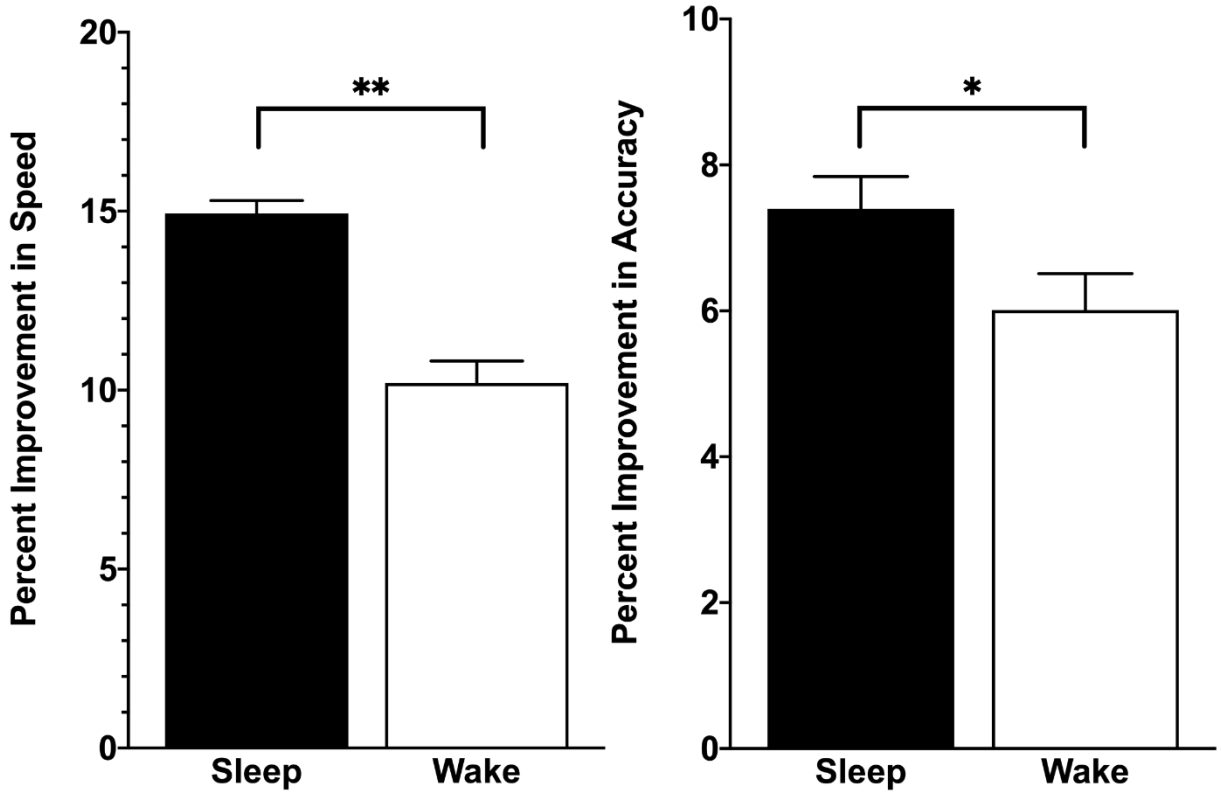

Figure 4. Behavioural improvements. Percent improvement in performance from before to after an interval of either sleep or wake. The sleep group improved significantly more than the wake group in terms of both speed (**left**) and accuracy (**right**). ** indicates $p<0.001$, * indicates $p<0.05$. Error bars indicate standard error of the mean.

3.2. Macro-Sleep Architecture. Macro-sleep architecture was comparable between ToH and control sessions in terms of sleep efficiency, time in each sleep stage, wake after sleep onset (WASO), and number of awakenings. Sleep characteristics and statistical comparisons between ToH and control sessions are reported in **Table 1.** Briefly, no significant differences between ToH and control nights were observed for any of these measures.

Table 1. Descriptive statistics for sleep architecture and comparisons between Control and ToH nights.

	ToH Night		control Night			
	Mean	**SD**	**Mean**	**SD**	***t***	***p***
Sleep Efficiency (%)	87.59	7.70	88.32	6.55	-0.59	0.556
NREM1 (Min)	17.23	15.28	12.83	8.79	1.35	0.191
NREM2 (Min)	227.10	34.73	222.75	36.13	0.49	0.627
NREM3 (Min)	74.90	22.51	83.15	20.51	-1.82	0.083
REM (Min)	86.06	23.86	98.76	30.86	-1.89	0.074
TST (Min)	405.29	42.58	417.39	50.87	-1.39	0.182
WASO (Min)	42.01	30.11	38.15	21.65	0.60	0.555
Awakenings (#)	30.70	7.71	30.80	9.58	-0.04	0.966

Abbreviations: Minutes (Mins); Total Sleep Time (TST); Wake After Sleep Onset (WASO).

3.3. REM Analysis. There were no significant changes in the characteristics of rapid EMs from the control night to the ToH night. Descriptive statistics and comparisons are reported in **Table 2.**

Table 2. Descriptive statistics and comparisons between Control and ToH nights for EM features observed during REM sleep.

	ToH Night		Control Night			
	Mean	**SD**	**Mean**	**SD**	***t***	***p***
Number of EMs (Total)	770.50	426.54	775.10	386.28	-0.06	0.952
Number of EMs in Bursts	732.75	414.71	734.10	366.66	-0.02	0.985
Number of Isolated EMs	37.75	23.26	41.00	23.26	-0.57	0.574
% of EMs in Bursts	94.67	2.11	94.49	1.48	-0.33	0.748
Burst Duration (Mins)	12.54	4.18	13.10	5.13	-1.56	0.134
Burst Intensity (Levels)	3.95	0.84	3.99	0.94	-0.31	0.762
Burst Density (#/Min)	1.84	0.29	1.78	0.30	0.77	0.454

Abbreviations: Eye Movements (EMs); Minutes (Min)

3.4. Changes in EEG power time-locked to EMs: ToH vs. Control night. ERSP analyses were conducted on the EEG time-locked to EMs that occurred either in bursts (phasic REM sleep), or in isolation (tonic REM sleep). Results are displayed in **Table 3** and **Figure 5**. In general, several clusters in the theta (~4-8 Hz) and sensorimotor rhythm (SMR; ~8-16 Hz) bands across midline channels were significantly greater at the ToH night compared to the control night, whereby differences in the SMR

tended to be more posterior. Specifically, for EMs in phasic REM sleep, significant differences were observed in the theta band at Fpz, Cz and Oz, and for the SMR at Oz. Power differences were also observed for EMs in tonic REM sleep in the theta band at Fpz, Cz, Pz and Oz, and for the SMR at Cz, Pz and Oz.

Table 3. Significantly greater power on the ToH compared to the control night for EEG power time-locked to EMs that occur either in bursts (i.e., phasic REM) or in isolation (i.e., tonic REM).

Eye Movements Bursts in Phasic REM sleep					
Channel	**Band**	**Peak (Hz)**	**Time (ms)**	***Z***	***p (FDR)***
Fpz	Theta	2.40	1015	2.01	0.043
Cz	SMR	8.34	773	2.20	0.027
Oz	Theta	7.63	1007	2.53	0.022
Oz	SMR	16.19	828	2.24	0.025
Isolated Eye Movements in Tonic REM sleep					
Channel	**Band**	**Peak (Hz)**	**Time (ms)**	***Z***	***p (FDR)***
Fpz	Theta	3.20	1164	2.76	0.005
Cz	SMR	9.65	-699	2.87	0.008
Cz	SMR	14.68	-582	2.53	0.011
Pz	SMR	13.87	-644	2.24	0.025
Oz	SMR	13.47	-519	2.83	0.020
Oz	Theta	4.61	-394	2.50	0.048
Oz	Theta	6.53	-1058	2.50	0.048
Oz	SMR	12.06	-1097	2.42	0.045
Oz	Theta	6.23	734	1.97	0.047

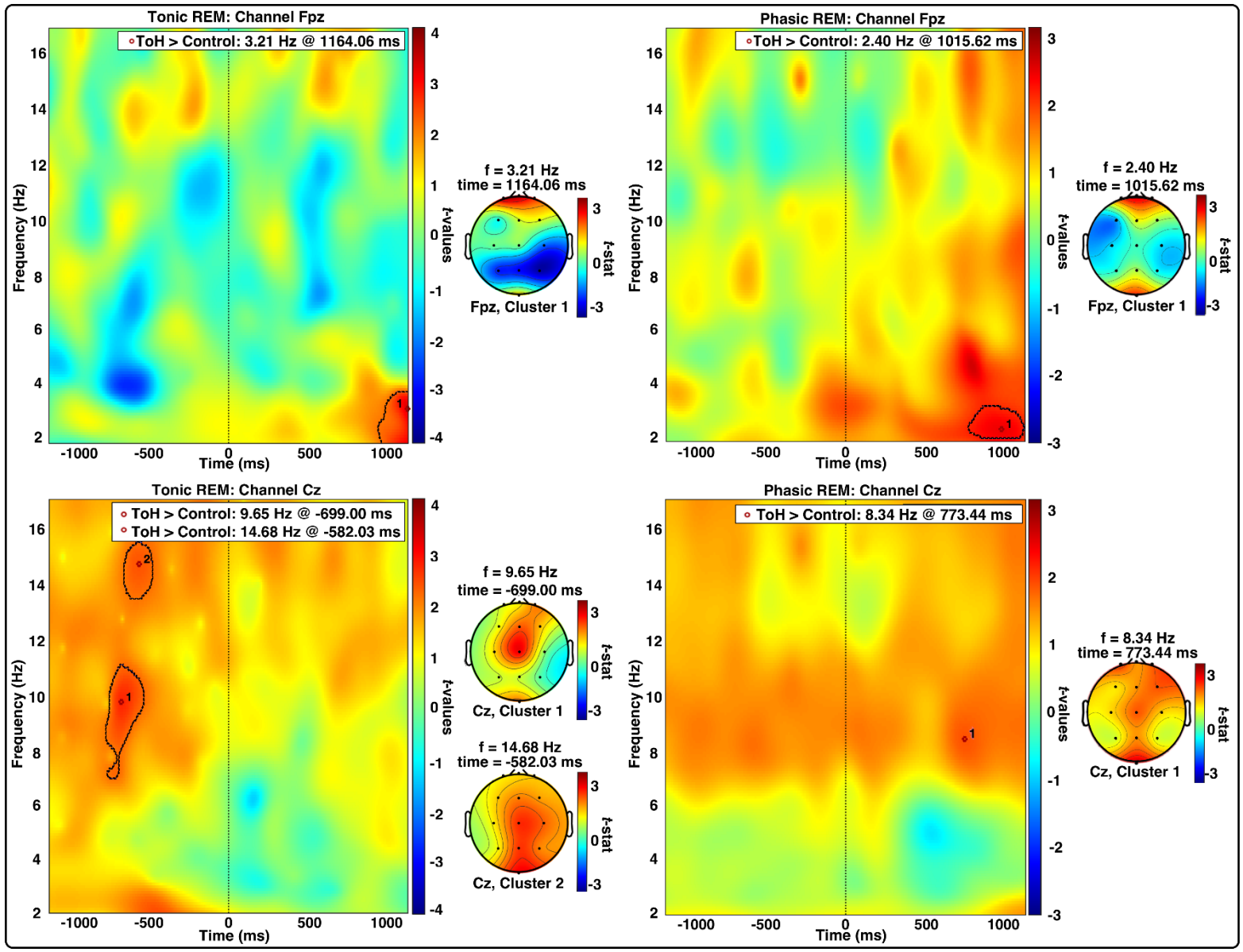

Figure 5. ERSP power differences across nights. Significant differences in ERSP power from the ToH night to the control night, for tonic (**left column**), and phasic (**right column**) REM sleep, at Fpz (**top row**) and Cz (**bottom row**). Adjacent topographic plots illustrate the distribution of the effect in that frequency and time point over the scalp. Borders drawn around the peak of significant clusters show the extent of the clusters. The peak for phasic EMs at Cz is significant at the peak level, corrected for the entire spectrogram.

3.5. Phasic vs. Tonic REM sleep. Night (ToH night, control Night) by EM type (Bursts, Isolated) 2 x 2 ANOVAs were used to follow-up the ERSP analyses in order to directly compare changes in EEG power time-locked to burst *vs*. isolated EMs from the ToH to control night. A consistent pattern of significant night by EM type interactions (**Figure 6**) were observed for clusters at central (Cz SMR cluster 1: $F(1, 38) = 11.24$, $p = 0.002$, $\eta^2 = 0.23$; Cz SMR cluster 2: $F(1, 38) = 10.59$, $p = 0.002$, $\eta^2 = 0.22$), parietal (Pz SMR: $F(1, 38) = 4.661$, $p = 0.037$, $\eta^2 = 0.11$) and occipital sites (Oz SMR: $F(1, 38) = 7.61$, $p = 0.009$, $\eta^2 = 0.17$).

Post-hoc tests showed that during the control night, power was consistently and significantly greater for burst *vs*. isolated EMs (Cz SMR cluster 1: $t(19) = 3.72$, $p = 0.0001$, $d = 1.00$; Cz SMR cluster 2: $t(19) = 2.20$, $p = 0.040$, $d = 0.63$; Pz SMR: $t(19) = 3.31$, $p = 0.004$, $d = 0.82$; Oz SMR: $t(19) = 2.66$, $p = 0.015$, $d = 0.79$). Power did not differ between burst and isolated EMs on the ToH night for all (all $p \geq 0.258$) but SMR power at Cz (cluster 2; $t(19) = 2.39$, $p = 0.027$, $d = 0.65$), whereby power for isolated surpassed burst EMs from control night to ToH night. In addition, power was consistently and significantly greater during the ToH night *vs.* control night for isolated EMs time-locked to power in the SMR (Cz cluster 1: $t(19) = 2.68$, $p = 0.015$, $d = 1.14$; Cz cluster 2: $t(19) = 2.40$, $p = 0.027$, $d = 1.00$; Pz: $t(19) = 2.58$, $p = 0.018$, $d = 0.74$; Oz: $t(19) = 3.24$, $p = 0.004$, $d = 1.19$). No significant differences in power were observed between ToH night *vs.* control night for burst EMs (all $p > 0.155$).

The above significant interactions were found only at the SMR frequency range, and all were from peaks that were identified during tonic REM sleep. No other significant interactions were observed. Specifically, no significant interactions were observed for clusters found in either the theta frequency range (all $p > 0.086$), or over peaks that were identified during phasic REM sleep (all $p > 0.14$). However, several main effects were observed, whereby theta power was

greater during phasic vs. tonic REM sleep, regardless of whether the peak was originally derived from phasic REM sleep (Fpz $F(1, 38) = 64.61$, $p < 0.001$, $\varepsilon = 0.63$) or from tonic REM sleep (Fpz $F(1, 38) = 68.64$, $p < 0.001$, $\varepsilon = 0.64$).

To summarize these main ERSP analyses and follow-up comparisons (phasic vs. tonic), we show that theta power and SMR power is higher on the ToH vs. Control. Additionally, theta power is higher overall across phasic and tonic REM sleep, but power in the SMR increases from the control night to the ToH night in tonic REM sleep, whereas SMR is relatively stable from night-to-night in phasic REM sleep.

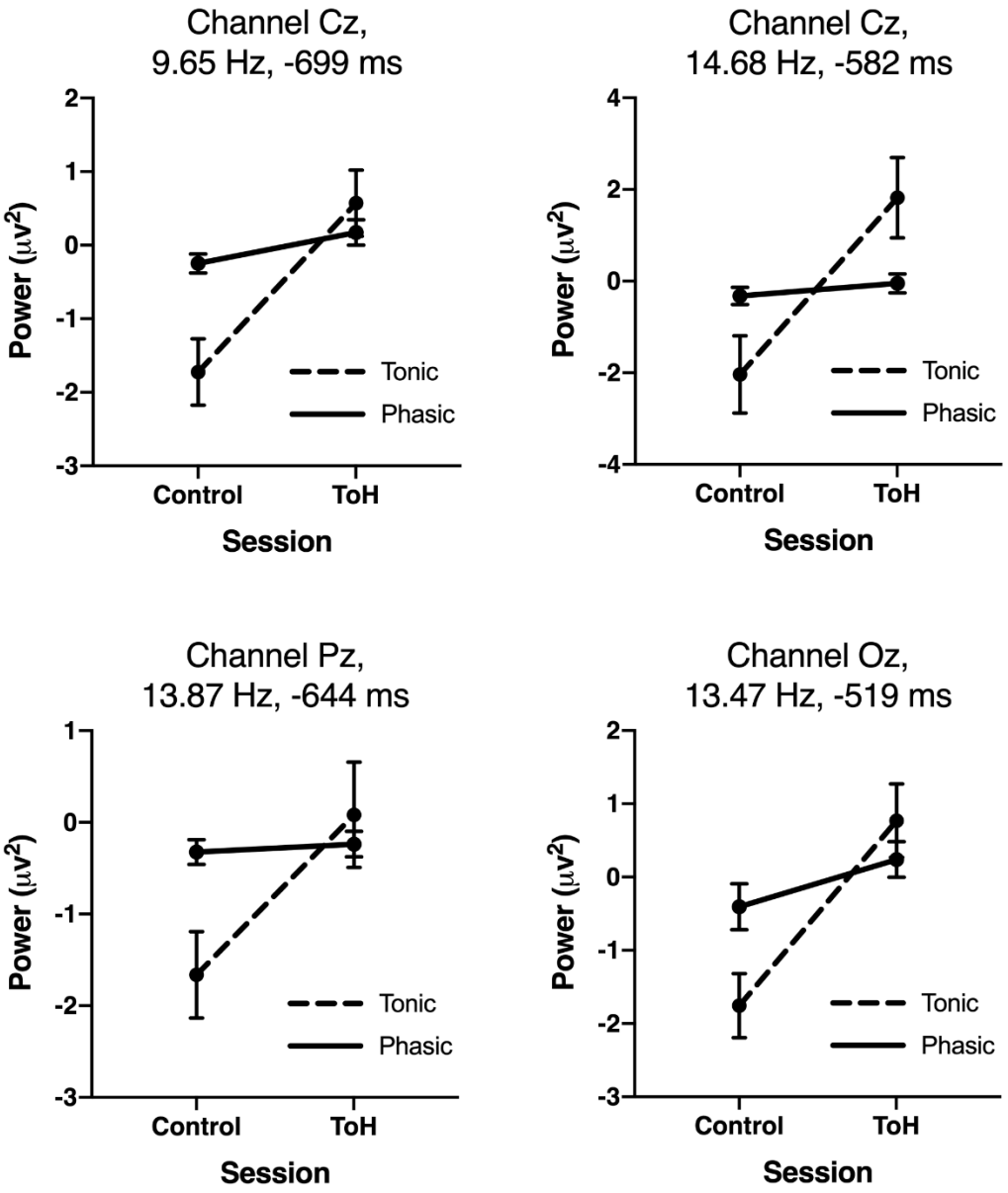

Figure 6. SMR power changes across nights between phasic and tonic REM sleep. Significant night (control, ToH) by EM type (burst, isolated) interaction effects at central, parietal, and occipital areas. SMR power time-locked to EMs occurring in phasic REM sleep remained stable from control to the ToH night, whereas power time-locked to isolated EMs in tonic REM sleep increased from the control to ToH night. Error bars indicate standard error of the mean.

3.6. Brain-Behaviour relationships. Finally, we assessed brain-behaviour relationships with performance improvements among significant clusters from the above ERSP analyses. Improvements on both speed and accuracy were positively correlated with percent change in power

from the control to the ToH night for EMs that occurred during phasic REM sleep (**Figure 7**). This was observed regardless of whether the peaks were extracted from differences in phasic REM sleep (Fpz speed: $r(18) = 0.45$, $p = 0.047$; accuracy: $r(18) = 0.64$, $p = 0.002$; and Cz accuracy: $r(18) = 0.57$, $p = 0.008$), or tonic REM sleep (Fpz speed: $r(18) = 0.477$, $p = 0.034$; accuracy: $r(18) = 0.44$, $p = 0.050$; Cz accuracy: $r(18) = 0.518$, $p = 0.019$). By contrast, the changes in EEG power time-locked to eye movements during tonic REM sleep were not significantly associated with behavioural improvements (all $p \geq 0.098$ for accuracy; $p \geq 0.073$ for speed).

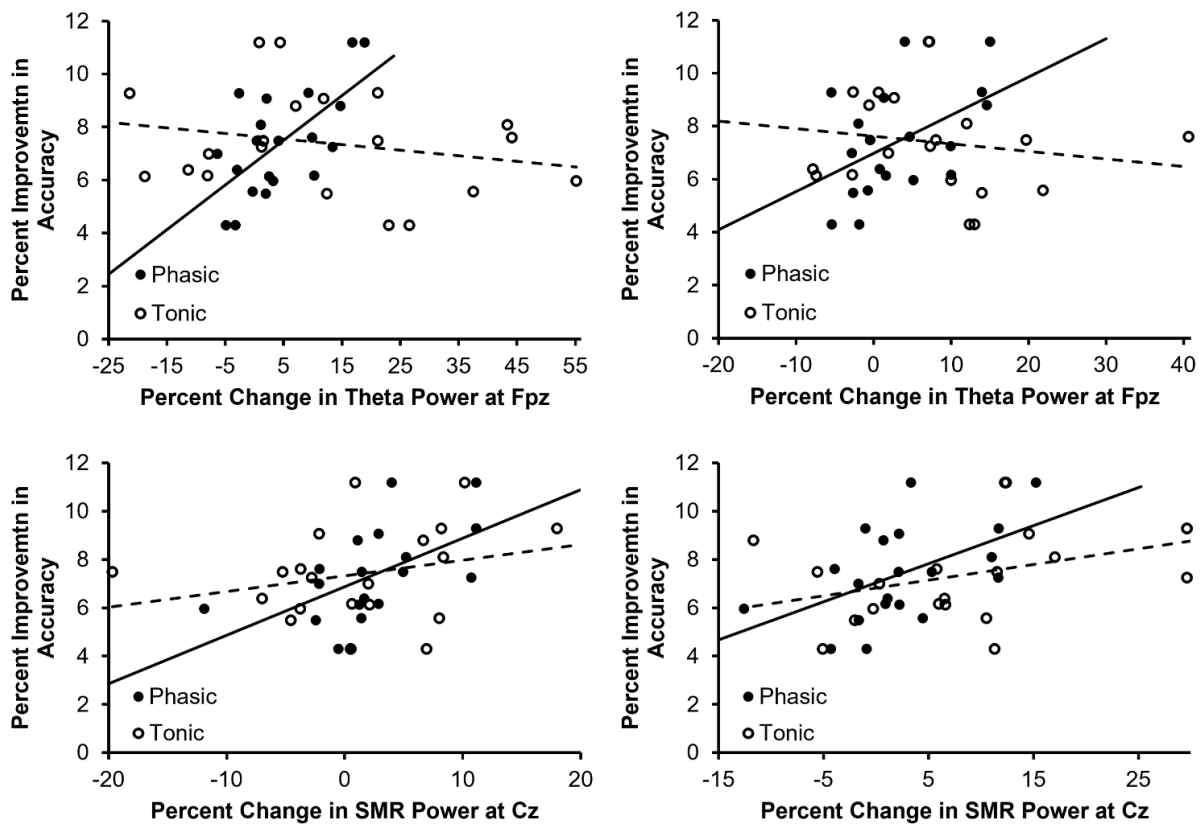

Figure 7. Brain-behaviour relationships. Correlations between behavioural performance improvements and changes in time-frequency power (from control to ToH night), for EMs occurring in phasic and tonic REM sleep. Theta (Top) and SMR (Bottom) Power were both positively correlated with phasic REM only, regardless of whether the power clusters were extracted from the phasic (left) or tonic (right) REM state. Solid and dotted lines reflect the line of best fit for EMs occurring in phasic and tonic REM sleep, respectively.

4. Discussion

EMs during REM sleep have been linked to the consolidation of cognitively complex novel motor skills (Buchegger et al., 1991; Buchegger & Meier-Koll, 1988) and to cognitive strategies (Maquet et al., 2000; Nielsen et al., 2015; Peigneux et al., 2003; Smith et al., 2004, 2004; Smith & Weeden, 1990). The benefit of sleep for this type of procedural memory has been frequently observed in studies which have employed the ToH (Brand et al., 2010; Fogel et al., 2015; Nielsen et al., 2015; van den Berg et al., 2019, 2021, 2023), although the neural activity that accompanies rapid EMs during REM sleep has not been thoroughly examined. However, studies in rodents have shown that the theta rhythm during REM sleep is implicated in memory for novel environments, spatial navigation and reward/avoidance learning (Boyce et al., 2016; Fogel et al., 2009; Jones & Wilson, 2005; Poe et al., 2000). In humans, one recent study employing an ERSP approach revealed that theta power time-locked to EMs was associated with procedural aspects of learning a second language (Thompson et al., 2021). Apart from this, the EEG correlates of memory consolidation for which EMs are a marker are largely unknown. Moreover, there is limited evidence on the functional relevance for the distinction between phasic and tonic REM sleep, however some evidence suggests that phasic and tonic REM states play functionally different roles for the consolidation of procedural memory (Bothe et al., 2019). In the present study, we employed EM detection and ERSP analyses to identify how the neural rhythms during phasic and tonic REM sleep are associated with the consolidation of procedural memory for cognitive strategies necessary for problem-solving skills.

In summary, here we showed that: **1)** behavioural improvements on the ToH were greater following a period of sleep *vs*. wake; **2)** when comparing the ToH learning night to the non-learning control night, ERSP analyses revealed that REM sleep theta and SMR power time-locked to EMs were increased for both phasic and tonic REM sleep; **3)** REM sleep theta and SMR power

time-locked to EMs were generally greater during phasic than tonic REM sleep (*i.e.*, at baseline), whereas SMR power time-locked to isolated EMs in tonic REM sleep increased significantly from the non-learning control night to the ToH night; finally, **4)** changes (from the control to the ToH night) in theta power and changes in the SMR, time-locked to EMs during phasic REM sleep, were positively correlated with overnight improvement.

4.1. REM sleep Theta. We observed increased power differences (ToH night – control night) in the theta frequency band time-locked to both tonic, isolated EMs and to phasic EM bursts. It is important to note that the human analog to rodent REM theta is typically thought to extend into slightly lower frequencies (approximately 2 Hz < 6 Hz; Bódizs et al., 2001; Clemens et al., 2009, 2013; Frauscher et al., 2020; Moroni et al., 2007; Sato et al., 1997). We also observed correlations between these changes in prefrontal theta power from the control to ToH night and improved ToH performance. Thus, the learning-related differences in slow theta rhythms observed here may reflect sawtooth waves, implicating them in memory consolidation processes for problem-solving skills. Importantly, this EEG power is above the frequencies (0.2-2 Hz, maximal at time = 0), that could be attributed to artifacts from the EMs (**Figure 2**) themselves (Tan et al., 2001). In addition to theta over prefrontal areas, we observed greater theta power differences across central-parietal-occipital derivations time-locked to both tonic isolated EMs and phasic EM bursts.

These results suggest that theta activity (observed most strongly over prefrontal derivations) is associated with consolidation of procedural memory involving cognitive strategies used for problem solving. Studies in both rodents (Boyce et al., 2016; de Almeida-Filho et al., 2021; Jones & Wilson, 2005; Poe et al., 2000) and humans (Durrant et al., 2015; Picard-Deland et al., 2021; Thompson et al., 2021) have implicated REM theta in memory consolidation. In rodents, theta rhythms are thought to reflect information transfer from hippocampal to neocortical areas

(Louie & Wilson, 2001) and decision-making (Seeley et al., 2016). In humans, frontal REM theta power has been implicated in second language-learning (Thompson et al., 2021), in schema-conformant memory consolidation (Durrant et al., 2015), and in dreams related to motor skill learning (Picard-Deland et al., 2021). We provide further support for a role of prefrontal REM theta for memory consolidation in humans, particularly for procedural memory that involves cognitive strategies necessary for problem solving. Furthermore, these results suggest that EMs during REM sleep are electrophysiological markers of this underlying process. Indeed, phasic REM theta power was not only greater at the ToH night compared to the non-learning control night, but was also associated with behavioural improvements.

4.2. The Sensorimotor Rhythm (SMR). EEG frequencies in the SMR frequency range during REM sleep cannot be attributed to spindles, given that by definition, spindles do not occur during REM sleep, and, the thalamus during REM sleep does not operate in the same bursting mode as in non-REM sleep, which produces sigma power associated with spindles (Contreras & Steriade, 1995; Destexhe et al., 1994). Given the wake-like qualities and similarities to quiet waking EEG, REM sleep ~8-16 Hz frequencies more likely reflect the SMR, and possibly reflect reactivation or replay. The SMR is present during quiet but attentive wakefulness (Chase & Harper, 1971), and can be as low as 8-12 Hz during both wakefulness and REM sleep (Marini et al., 2008). Motor skills can be improved by enhancing the SMR through neurofeedback (Sterman et al., 1970).

Here, we also observed greater SMR power following ToH compared to the non-learning control night at central, parietal, and occipital areas. In addition to changes in theta power, we show that the SMR during phasic REM sleep is correlated with behavioural improvements on procedural memory for cognitive strategies and problem-solving skills.

4.3. Phasic *vs.* Tonic REM sleep. Phasic and tonic REM sleep are neurophysiologically distinct (Grosser & Siegal, 1971), and the available (albeit limited) evidence suggests that both phasic and tonic REM sleep have dissociable functions with respect to memory consolidation (Bothe et al., 2019; Guerrien et al., 1989; Smith & Weeden, 1990). Though theoretical, it has been proposed that phasic REM sleep facilitates the hippocampal-neocortical dialogue (Bódizs et al., 2001; Hutchison & Rathore, 2015), while tonic REM sleep is implicated in pattern separation (Montgomery et al., 2008). Others propose that phasic REM sleep is associated with consolidating emotionally salient information, whereas tonic REM sleep is for contextualization of newly acquired memories (Simor et al., 2020). The literature remains scarce and speculative on the precise functions of these two states, and their associated neural correlates.

The present results provide intriguing evidence to suggest dissociable roles of phasic and tonic REM sleep for consolidating memory for cognitive strategies and problem-solving skills. Power from control to ToH nights over the SMR across central, parietal, and occipital channels showed a consistent difference between phasic and tonic REM sleep; whereas power at phasic REM sleep showed a relatively stable pattern from control to ToH nights, power at tonic REM sleep increased from control to ToH nights. These patterns suggest that sensorimotor information is persistently processed when time-locked to EMs during phasic REM sleep as compared to tonic REM sleep. By contrast, tonic REM sleep might play an idle or lesser function for memory consolidation if not exposed to a procedural-based strategy prior to sleep, but might become engaged when a novel cognitive procedural strategy requires consolidation.

4.4. Limitations. We employed a well-established protocol, commonly used to investigate the role of sleep for memory consolidation. However, it is not without its drawbacks. For example, there were time-of-day differences between when the Sleep and Wake groups were tested on the

ToH; the Sleep group was trained in the evening and retested in the morning, while the Wake group was trained in the morning and retested in the evening. Thus, we cannot rule out time-of-day effects for our behavioural results. However, our previous work, using the same task, carefully addressed this issue by comparing an AM-PM-AM group to a PM-AM-PM group, thus permitting both groups a sleep opportunity (van den Berg et al., 2019). Those findings showed that consolidation occurred regardless of testing time, or when the sleep opportunity occurred. In addition, in the present study, the changes in power at the ToH night were compared to a control night, suggesting that the consolidation benefit was due to sleep *per se*.

5. Conclusion

We demonstrate a benefit of sleep compared to a period of wake for consolidating procedural memories involving novel cognitive strategies required for problem-solving skills. Further, by employing a novel analysis approach to probe the functional significance of EMs during both phasic and tonic REM sleep, we also show that: power in theta and SMR bands are greater following learning (compared to a non-learning control); power in these frequency bands are higher during phasic REM sleep than during tonic REM sleep, however only SMR power increases after learning a novel cognitive strategy and does so only during tonic REM sleep, and; the increase in theta and SMR power during phasic REM sleep is associated with the consolidation of novel cognitive strategies.

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Chapter 3: Study 2

Sleep enhances consolidation of memory traces for complex problem-solving skills

Abstract

Sleep consolidates memory for procedural motor skills, reflected by sleep-dependent changes in the hippocampal-striatal-cortical network. Other forms of procedural skills require the acquisition of a novel strategy to solve a problem, which recruit overlapping brain regions and specialized areas including the caudate and prefrontal cortex. Sleep preferentially benefits strategy and problem-solving skills over the accompanying motor execution movements. However, it is unclear how acquiring new strategies benefit from sleep. Here, participants performed a task requiring the execution of a sequence of movements to learn a novel cognitive strategy. Participants performed this task while undergoing fMRI before and after an interval of either a full night sleep, a daytime nap, or wakefulness. Participants also performed a motor control task, which precluded the opportunity to learn the strategy. In this way, we subtracted motor execution-related brain activations from activations specific to the strategy. The sleep and nap groups experienced greater behavioural performance improvements compared to the wake group on the strategy-based task. Following sleep, we observed enhanced activation of the caudate in addition to regions in the hippocampal-striatal-cortical network, compared to wakefulness. This study demonstrates that sleep is a privileged time to enhance newly acquired cognitive strategies needed to solve problems.

Keywords: sleep, fMRI, memory consolidation, procedural memory, problem solving.

1. Introduction

The “eureka moment” for some of the most remarkable ideas, inventions and works of art in human history have manifested over a night of sleep. A few of the most famous anecdotal accounts include Albert Einstein’s theory of relativity, Dimitry Mendeleev’s inception of the periodic table, the discovery of insulin by Frederick Banting, Niels Bohr’s insight into the structure of the atom, and Larry Page’s inspiration for Google. There is indeed something special about sleep that facilitates the process of insight into the solution to a problem (Lewicki, Czyzewska & Hoffman, 1987; Walker et al., 2002; Stickgold & Walker 2004; Cai et al., 2009; Brand et al., 2010; Durrant et al., 2011; Sio, Monaghan & Ormerod 2013; Beijamini et al., 2014; Fogel et al., 2015; Monaghan et al., 2015; Lewis, Knoblich, & Poe 2018; Perdomo, Hofman, & Talamini 2018; van den Berg et al., 2019). Problem solving involves reasoning, planning, strategies and skills, which are important aspects of certain forms of procedural memory – the “how to” of long-term memory.

When a memory is initially acquired, is not fully stabilized or fully integrated. At the systems level, the newly encoded memory is stabilized through memory consolidation, which transforms the memory into a lasting, integrated, and more easily retrievable form. Sleep is becoming increasingly recognized as an optimal time for consolidating procedural memory and related skills (for reviews see Rasch & Born 2013; King et al., 2017), including memory involving the acquisition of novel cognitive strategies (Mandai et al., 1989; Smith & Weeden 1990; Smith & Wong 1991; Smith 1995; 1996; 2001; Plihal & Born 1997; Smith and Smith 2003; Fogel, Smith, & Cote 2007; Fogel et al., 2015; Nielsen et al., 2015; van den Berg et al., 2019). Still, it remains unclear how sleep transforms and enhances memory traces for novel strategies which are needed to solve problems. This was the main aim of the current study.

Given the multifaceted nature of procedural memory and related skills (Cohen et al., 2005; Robertson, 2009; King et al., 2017), several studies have employed experimental paradigms which disentangle the motor execution components from cognitive components (Van Hedger et al., 2015; Nagai et al., 2017; van den Berg et al., 2019; Conte et al., 2020). These studies suggest that sleep preferentially enhances the more cognitive aspects over the purely motor aspects (particularly when motor skills are acquired implicitly), thus suggesting that they rely on distinct neural substrates. One classic example of a strategy-based procedural task is the Tower of Hanoi (ToH). Solving the ToH requires the execution of a sequence of motor movements to learn the underlying cognitive strategy (*i.e.*, recursive logic; **Figure 1**). The overall ToH recursive solution consists of moving n disks from the source peg (*e.g.*, A) to the target peg (*e.g.*, C), while using the remaining peg (*e.g.*, B) as the "spare" peg. According to this logic, the key to solving larger, more complicated problems (*e.g.*, the 5-disk solution) can be solved by breaking it down into a series of small problems (*e.g.*, the 3-disk solution), which is repeated several times. There is only one optimal solution to the problem (*i.e.*, using the minimum number of moves). Our recent work has shown that participants extrapolated the fundamental strategy of a simple 3-disk version of the ToH (*i.e.*, a 7-move solution), to a more complicated 5-disk version (*i.e.*, 31-move solution), but only if they slept during the retention interval (van den Berg et al., 2019). By contrast, there was no preferential benefit of sleep vs. wake for the motor movements required to execute the solution to the problem, suggesting that sleep processes the recursive strategy, which is not achieved through sleep-related enhancement of the motor sequence *per se*.

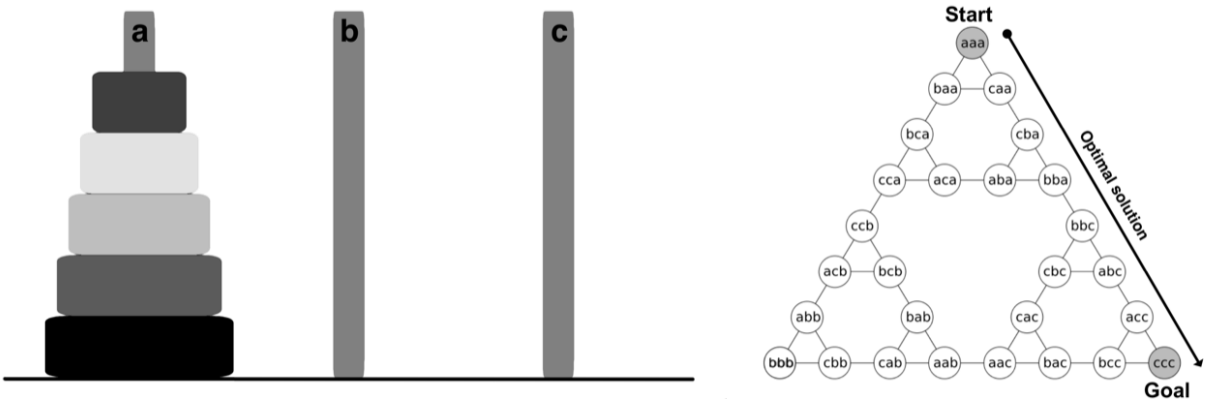

Figure 1. The 5-disk version of the Tower of Hanoi (left) and the graphical representation of the optimal solution for the 3-disk version (right). Each node represents the distribution of the disks, and each letter represents one disk (*i.e.,* the *Start* node configuration *aaa* contains all three disks on the *a* peg; whereas the *caa* peg immediately below has two disks on the *a* peg and one disk on the *c* peg). Disks are listed from left to right in order of increasing size, and each edge represents a move from one configuration to another. The puzzle starts off with all 3 disks on the left-most peg (aaa), ending in the goal configuration with all 3 disks on the right-most peg (*ccc*). Only one series of moves results in the optimal 7-move solution for the 3-disk problem. More complicated versions (*e.g.*, the 5-disk problem) can be solved by recursively applying the logic needed to solve the 3-disk problem, iteratively, several times. Figure adapted from Fogel et al. (2015).

Despite behavioural advances in understanding sleep-facilitated problem solving, little is known about the related neurobiological substrates and processes. Existing knowledge regarding the neural correlates of sleep-related procedural memory consolidation largely comes from studies investigating motor sequence learning. More specifically, brain areas in the cortico-striatal-hippocampal network are recruited during the acquisition of a novel motor sequence. This memory trace is transformed (Fogel et al., 2017) and strengthened as a function of both practice (Doyon et al., 2002; Ungerleider, Doyon, & Karni 2002) and time (Lehéricy et al., 2005). Recruitment of the putamen is central during the consolidation of memory for newly acquired motor sequences, which is further strengthened when the subsequent retention interval contains sleep vs. wake, resulting in enhanced performance (Debas et al., 2010).

However, the putamen does not act in isolation. Sleep-dependent consolidation of newly acquired motor sequences can be dissociated into a motor aspect which is reliant on the putamen,

and a spatial aspect which relies on the hippocampus (Albouy, Fogel, et al., 2013; Albouy et al., 2015). Evidence points to a competitive interaction between these brain areas (Albouy, King, et al., 2013), and interestingly, this suggests a role of the hippocampus for procedural memory consolidation when the task has a spatial component, and when consolidation is preferentially enhanced by sleep. Accordingly, the hippocampus seems to play an important role in initial procedural motor sequence learning, and acts in a dissociable way from typically motor-related brain areas (*e.g.*, the putamen) following a period of consolidation, particularly one that contains sleep.

We hypothesize that an analogous, sleep-related consolidation process might take place for motor sequences that also involve complex problem-solving skills. A network of brain structures including the hippocampus, prefrontal cortex (PFC), and the striatum support goal-directed and decision-making behaviour (Poldrack et al., 1999; Destrebecqz et al., 2005; Lappin et al., 2009; Pezzulo et al., 2014; Bick et al., 2019). These regions are recruited when solving the ToH and similar tasks, with the caudate playing a key role in this process (Doyon et al., 1996; Owen et al., 1996; Dagher et al., 1999; Rowe et al., 2001; van den Heuvel et al., 2003; Unterrainer & Owen 2006; Stocco & Anderson 2008). For example, activation of the caudate nucleus is observed only during active planning of a novel action versus continuous rule-following (Monchi et al., 2006), suggesting a role of the caudate for novel and potentially higher-order learning. The caudate is also implicated in skills required to perform the ToH, including error detection and response inhibition (Rubia et al., 2003; 2007; Stevens et al., 2009; Aron et al., 2003; Hochman et al., 2015), attentional control (Cieslik et al., 2015), associative learning (Jueptner et al., 1997; Bick et al., 2019), algebraic problem-solving (Stocco & Anderson 2008),

automizing implicitly learned information (Lehéricy et al., 2005), and reward learning (Elliott, Friston, & Dolan 2000; Lappin et al., 2009).

In summary, the neural correlates for the sleep-related memory consolidation of motor skills are relatively well-known. By contrast, the neural correlates of sleep-related memory consolidation for strategy and problem-solving skills are less clear. To understand this further, two versions of the ToH task adapted for functional magnetic resonance imaging (fMRI) were employed: 1) the "classic" ToH, and 2) a modified control (CTL) version of the task. This CTL version visually appears identical to, and is operated in the same way as, the ToH, but participants instead execute a series of random movements. In this way, we could subtract out brain activations associated with motor execution movements required to perform the ToH task from the activations related to the cognitive strategy itself. It was hypothesized that: 1) the greatest benefit in ToH performance would be from sleep, and, 2) a sleep-dependent increase in brain activation would be observed in structures known to be involved in reward learning, planning, and problem solving (*e.g.*, the hippocampus, caudate, motor cortex, and frontal cortex).

2. Methods

2.1. Participants. Power analyses based on similar studies from our group (*e.g.*, Fogel et al., 2014), with alpha = 0.05, indicates that we would need a sample size of at least n = 15 for Sleep, Nap, and Wake groups to obtain 80% power when detecting a significant effect for our primary analyses of the behavioural and fMRI data. This is based on an effect size $f = 0.9$ for behavioural effects and a more conservative estimate of $f = 0.7$ for MRI effects. In order to ensure adequate power to control for multiple comparisons and account for bad/missing data, we collected $n = 20$ per group.

All participants were right-handed, in good health, non-shift workers, and were not taking medications known to interfere with sleep. They had regular sleep schedules (within the hours of

10 PM to 9 AM), a body mass index <30, and no history of sleep disorders. Participants had no history of chronic pain, seizures or head injury and no mobility problems with their hands and fingers. To be included, participants had to report normal, or corrected-to-normal vision, score <10 on the Beck Depression (Beck & Beamesderfer 1974) and the Beck Anxiety (Beck et al., 1988) inventories, and have no signs of sleep disorders indicated by the Sleep Disorders Questionnaire (Douglass et al., 1994). Participants were also excluded from the study if they reported having previous experience with the ToH, or similar tasks.

The first night of polysomnography (PSG) recording served as an acclimatization and sleep disorder screening night, which took place one week prior to the experimental session. Based on the results of the screening night, participants who had poor sleep quality (*i.e.*, sleep efficiency (SE) < 80%), more than 10 respiratory events per hour (indicating signs of sleep apnea), or any other unusual behaviours during sleep that might indicate the presence of parasomnias, were excluded from further participation in the study. To ensure compliance with the experimental protocol, all participants were asked to wear a wrist-worn Motionlogger actigraph (Ambulatory Monitoring Inc., Ardsley, NY, U.S.A.) and to complete a log of their daily activities and sleep habits to verify that they maintained a regular sleep schedule for the duration of the study.

Five participants were excluded from the study: four participants for non-compliance with the study protocol based on irregular sleep schedules, and one who voluntarily dropped out of the study following the acclimatization and screening night. The final sample consisted of 60 healthy young adults (34 females) between the ages of 20 and 35 years (M = 24.38, SD = 4.44). Following screening, all participants were randomly assigned to either the Sleep (n = 20), Nap (n = 20), or Wake (n = 20) condition.

2.2. Ethics Statement. All participants were given a letter of information, provided informed written consent before participation, and were financially compensated for their participation. All study procedures were approved by Research Ethics Boards at the University of Ottawa and The Royal's Institute of Mental Health Research (IMHR).

2.3. Experimental Design. Following screening, participants returned to the laboratory and underwent the experimental testing session (**Figure 2**). Upon arrival, participants performed eight trials of the ToH and four trials of the CTL task while being scanned in the MRI (i.e., training session). This training session was then followed by either: 1) an 8-hour overnight PSG recording (Sleep condition), 2) a 90-minute daytime PSG recording (Nap condition), or 3) an 8-hour daytime wake period (Wake condition). After a >30-minute period to allow the effects of sleep inertia to dissipate, participants completed four trials of both the ToH and CTL tasks again, while being scanned in the MRI (*i.e.*, retest session).

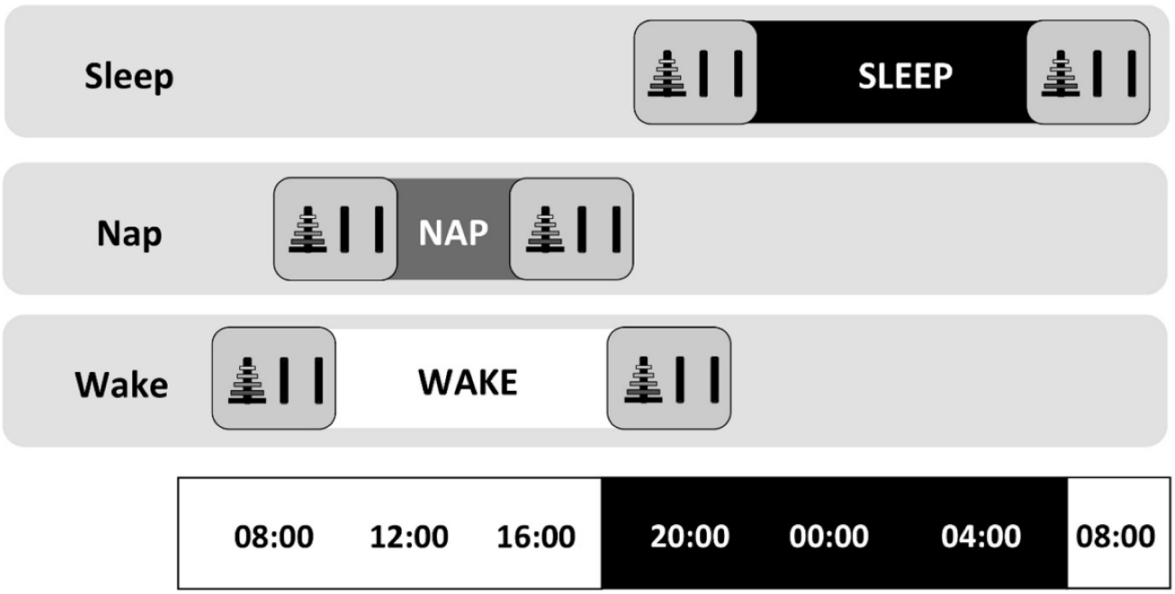

Figure 2. Overview of experimental protocol in the Sleep, Nap and Wake conditions. **Sleep Condition:** Participants arrived at the laboratory at approximately 08:00 PM, were trained on the classic ToH. and performed the CTL task. Participants then slept in the lab from approximately 11:00 PM to 07:00 AM while their sleep was recorded via PSG. Upon awakening, participants were retested on the ToH and performed the CTL task. **Nap Condition:** Participants arrived at the lab at approximately 10:30 AM, were trained on the ToH and performed the CTL task, and slept in the lab from approximately 01:00 PM to 02:30 PM while their sleep was recorded via PSG. Upon awakening, participants were retested on the ToH and performed the CTL task. **Wake Condition:** Participants arrived at the lab at 08:00 AM and were trained on the ToH and performed the CTL task. Participants then left the lab for the day with instructions not to nap (confirmed via actigraphy). Participants returned to the lab at 08:00 PM and were retested on the ToH and performed the CTL task. All sessions of the ToH and CTL tasks were completed while obtaining functional blood oxygen level dependent (BOLD) images using a block design (see section "*MRI Imaging Acquisition and Analysis*" for details). During the ToH testing and retesting sessions, participants performed a 5-disk version of the classic ToH task in addition to CTL task, to control for random motor movements (see section "*Behavioural Tasks and Analysis*" for details). The order of the ToH and CTL tasks was counterbalanced across participants.

2.4. Behavioural Tasks and Analysis. The present study used two computerized variants of the classic Tower of Hanoi (ToH) task, coded in MATLAB R2016a (Mathworks Inc., Natick, MA, USA) using the Psychophysics Toolbox extension v3.0.12 (Brainard 1997; Kleiner, Brainard, and Pelli 2007), adapted for MRI, including: 1) the "classic" ToH, and, 2) a modified control (CTL) version of the task.

2.4.1 Tower of Hanoi Task. A 5-disk version of the ToH task was used in the present study. This task requires the participant to learn and execute an underlying cognitive strategy (i.e., recursive logic), acquired through trial-and-error, with the aim of solving the puzzle with a minimum number of moves, *i.e.*, the optimal solution (**Figure 1**). The visual appearance of the task includes three identical pegs equally spaced apart, beginning with 5 disks stacked on the far-left peg in ascending order of size (largest disk on the bottom, smallest disk on the top). Participants were instructed that the objective of the task, for each trial, was to transfer all disks, moving them one at a time, from the beginning position on the far-left peg, to the goal configuration on the far-right peg stacked in the same ascending order, while obeying several simple constraints: 1) only one disk can be moved at a time, 2) only the upper-most disk from any one of the three pegs can be moved, and, 3) a disk can only be placed on either an empty peg, or on another disk that is larger in size.

Participants are informed of these constraints prior to performing the task. An MR-compatible fibre optic response button box (model HHSC-2x4-C; Current Designs Inc., Philadelphia PA, USA) comprising four push buttons located in a horizontal row at equal distance from each other was used to operate the task. Participants were instructed to control the on-screen movement of the disks as fast and as accurately as possible, by using the response box with their index finger, middle finger and ring finger on their right hand only, corresponding to the left-most, centre and right-most peg, respectively. Each button-press controlled the movement of disks from and to one of the three pegs.

Each trial was followed by a 20-second rest period. A trial of the ToH task ended when all five disks were stacked in ascending order on the far-right peg, or if the maximum number of moves was reached before successful completion of the task. The maximum number of moves

was set at three times the optimal number of moves ($2^N - 1$, where N is the number of disks, *i.e.*, 25 - 1 = 31). Therefore, the maximum number of moves for the 5-disk task, for each trial, was set at 93 moves. For the rest periods, participants were shown all three pegs but with no disks visible, and they were instructed to abstain from pressing any buttons during this time.

The main variables of interest for the ToH were the number of errors (*i.e.*, number of invalid moves, *e.g.*, mistakenly placing a larger disk onto a smaller disk), speed (time to complete each ToH trial), accuracy (Mean Absolute Percentage Error of valid moves; MAPE), and speed:accuracy trade-off (time/number of valid moves; SATO). The MAPE for n trials was calculated as follows:

$$MAPE=100-(1/n)*\sum(|number\ of\ moves- optimal\ number\ of\ moves|/(number\ of\ moves))*100$$

In this way, the MAPE can be interpreted as the percentage difference from perfect performance for valid moves (*e.g.*, 100% reflects perfect performance, whereas 50% reflects making twice as many moves as perfect performance, and 0% represents an infinite number of moves). The % improvement for all variables was calculated by taking the performance in the first retest trial minus performance in the last training trial, divided by performance in the last training trial, multiplied by 100:

$$\%\ improvement=((Retest-Training)/Training)*100$$

2.4.2. Tower of Hanoi Control Task. The purpose of the control (CTL) task was to control for (*i.e.*, subtract out) brain activations related to the motor executions and visual characteristics of the ToH. The CTL task was visually identical to, and was operated in the same way as, the ToH, but participants instead executed a series of random movements. Although these random movements adhered to the constraints of the classic ToH task (so as not to make illegal moves), the moves were otherwise random. Each random move was guided by a pair of

visual cues appearing above the pegs to indicate the selection of a disk from (indicated by a green dot), and to (indicated by a red dot) one of the three pegs. Each trial of the CTL task ended when a total of 31 randomly guided moves were completed, corresponding to the number of moves for the optimal solution to complete the 5-disk ToH task. Importantly, the movements did not systematically follow the movements required to learn the underlying strategy needed to complete the ToH (*i.e*., recursive logic), but still required the same type of motor execution as the ToH (*e.g*., speed and number of movements per trial). Participants performed four trials of the CTL task, where each trial was followed by a 20-second rest period.

2.5. Behavioural Analysis. All behavioural statistical analyses were carried out using SPSS Statistics version 25 (IBM, Armonk, New York, U.S.). To ensure that learning did take place during the training session on the ToH task, repeated measures analysis of variance (ANOVA) for Trial (trials 1 to 8) were conducted for errors, speed, accuracy, and SATO. To address our main hypotheses, and to explore whether sleep facilitated performance on the ToH task, separate one-way analysis of variance (ANOVA) with condition (Sleep, Nap, Wake) as a between groups factor were performed on the % improvement in errors, speed, accuracy, and speed-accuracy trade-off. A significant effect of condition was followed-up by planned comparison independent t-tests. Skewness in the distributions of the measures was normalized by taking the square root of the raw scores where appropriate.

2.6. Polysomnographic Recording and Analysis

2.6.1. PSG Recording Parameters. In-laboratory PSG was recorded with Embla N7000 32-channel amplifier system (Natus, Pleasonton, CA, USA) sampled at 500 Hz. EEG (Fp1, Fpz, Fp2, F3, Fz, F4, C3, Cz, C4, P3, Pz, P4, and Oz) and EOG (placed on the outer canthus of the eyes) were referenced to Fpz online with Afz ground, placed according to the international 10-20

system (Jasper 1958). A submental EMG channel was recorded as a bipolar derivation. All EEG electrode impedances were reduced to < 5 KOhm.

2.6.2. PSG Analysis. Manual sleep stage scoring according to standard criteria (Rechtschaffen and Kales 1968; Iber et al., 2007) was completed by a single expert scorer using RemLogic analysis software (Natus, San Carlos, CA, USA). EEG and EOG were re-referenced offline to average mastoid derivations (M1 and M2). EEG was filtered from 0.3 to 35 Hz, EOG was filtered from 0.3 to 10 Hz and EMG was filtered from 10 to 100 Hz. The sleep variables of interest obtained from the PSG recording sessions included the total sleep time (TST), time in minutes spent in Stage 1 (NREM1) sleep, Stage 2 (NREM2) sleep, slow wave sleep (SWS), and rapid eye movement (REM) sleep, sleep efficiency, and wake after sleep onset (WASO). TST was calculated as the total time spent asleep between "lights off" and "lights on".

2.7. MRI Imaging Acquisition and Analysis

2.7.1. Recording Parameters. Functional magnetic resonance imaging (fMRI) data was collected on a Siemens Biograph mMR 3.0 Tesla MRI whole body scanner (Siemens, Erlangen, Germany) using a 12-channel head coil. Anatomical images were acquired using a standard 3D Multislice MPRAGE sequence (TR = 2300 ms, TE = 2.98 ms, TI = 900 ms, FA = 9º, 176 slices, FoV = 256 × 256 mm^2, matrix size = 256 × 256 × 176, voxel size = 1 × 1 × 1 mm^3). In addition, multislice T2-weighted functional MRI images were acquired during the ToH and CTL tasks (TR = 2.16 sec; TE = 30 ms, FA = 9º, 40 transverse slice, 3 mm slice thickness, 10% inter-slice gap, FoV = 220 x 220 mm^2, matrix size = 64 x 64 x 40, voxel size = 3.44 x 3.44 x 3 mm^3).

2.7.2. Preprocessing. Functional volumes were preprocessed and analyzed using SPM12 (www.fil.ion.ucl.ac.uk/spm; The Wellcome Centre for Human Neuroimaging, London, UK) implemented in MATLAB R2018a for OS X (Apple, Cupertino, CA). Anatomical images were

first roughly auto-oriented. Functional images for each participant were realigned to the first functional volume of the session, and coregistered to the T1-weighted anatomical image. The coregistered anatomical images were then segmented into grey matter, white matter and cerebrospinal fluid. Visual inspection of participant movement of both translations and rotations around x, y, and z was performed. Movement was within acceptable tolerances for all participants (*i.e.*, did not exceed 6 mm). Next, an average subject-based template was created using DARTEL in SPM12 and used to normalize all anatomical and functional images. Lastly, spatial smoothing was applied on all functional images (Gaussian kernel, 8 mm full-width at half-maximum; FWHM).

2.7.3. First-Level (within subject) Fixed Effects Analysis. The canonical hemodynamic response function (HRF), and its temporal and dispersion basis functions were estimated at the individual level using the General Linear Model (GLM) in a block-design (*i.e.*, task vs. rest). Slow drifts were removed from the time series using a high-pass filter with a cut-off period of 128 seconds. Serial correlations in the fMRI signal were estimated using an autoregressive (order 1) plus white noise model and a restricted maximum likelihood algorithm.

Specifically, these first-level analyses observed brain activations associated with problem solving (ToH) after subtracting out the motor movements (CTL) required to execute the strategy were used in the analysis (*i.e.*, ToH-CTL). Linear contrasts tested for the main effect of: 1) within the training session (ToH–CTL training) in order to assess which brain regions were initially recruited during learning, and, 2) the difference between the training and retest sessions [(ToH–CTL retest) – (ToH–CTL training)]. Each of these first-level (within subject) contrasts comprised of the complete basis set (a set of 3 contrasts: one for the HRF, and the temporal and dispersion basis functions), and were passed onto second-level (between groups) analyses (see

below), in order to examine the impact of the experimental condition of a retention interval of either sleep, nap or wake on memory consolidation of the memory trace.

2.7.4. Second-Level (between groups) Random-Effects Analysis. The resulting within-subject contrast images of interest from the first-level analysis, comprised of the informed basis set (contrasts for the HRF, temporal and dispersion basis functions) were entered into a second-level ANOVA to examine differences in activation between the: 1) Sleep vs. Wake groups, 2) Sleep vs. Nap groups, and, 3) Nap vs. Wake groups. This approach is advantageous as not only is amplitude of the canonical HRF accounted for, but also, the temporal derivative accounts for variations in the timing of the peak response, and the dispersion derivative accounts for variations in the width of the response (Henson & Penny, 2003; Henson, Rugg, & Friston, 2001). In this way, we could examine the HRF response for each group comparison without the assumption that the temporal and dispersion functions were constant. In order to determine the direction of the effect, we examined the contrast estimates and 95% confidence intervals for the HRF only, for each significant cluster. All group-level hypotheses were tested at a threshold of $p < 0.05$, controlling for multiple comparisons using False Discovery Rate (FDR) whole-brain correction.

2.8. Brain-Behaviour Relationships. Follow-up analyses assessed whether changes in behavioural performance were related to changes in brain activation in the post vs. pre retention interval (*i.e.*, Retest - Training). We employed univariate General Linear Models to test whether the association between performance measures (*i.e.*, offline gains in speed, accuracy) and changes in brain activation (from training to retest) in selected and significant regions of interest (*i.e.*, hippocampus, caudate nucleus, supplementary motor area and prefrontal cortex) differed as a function of condition (Sleep, Nap, Wake). Specifically, gains in performance (in separate

models for accuracy and speed for each brain region of interest) were entered as the dependent variable, whereas condition (Sleep, Nap, Wake) was entered as the independent variable, with changes in brain activation (retest-training) as a covariate. The 2-way interaction term with the covariate (condition x activation) was used to determine if the relationship between gains and brain activation differed among the 3 conditions. To illustrate the significantly different relationships between performance gains and changes in brain activation between the conditions, the predicted gains scores were plotted against activation changes.

3. Results

3.1. Behavioural Data. First, in order to verify that all groups improved (*i.e.*, learned) during the training session, a one-way repeated measures ANOVA revealed that there was a significant improvement in errors ($F(7,413) = 20.80$, $p < 0.0001$, $\eta^2 = 0.26$), speed ($F(7,413) = 61.52$, $p < 0.0001$, $\eta^2 = 0.51$), accuracy ($F(7,413) = 12.65$, $p < 0.0001$, $\eta^2 = 0.17$) and SATO ($F(7,413) = 123.33$, $p < 0.0001$, $\eta^2 = 0.68$) over the course of practice during this initial learning phase (**Supplemental Figure S1**).

Next, we investigated the impact of sleep on performance improvements from training to retest (**Figure 3**). A one-way ANOVA revealed a statistically significant difference between the Sleep, Nap, and Wake groups in % improvement for speed ($F(2,57) = 51.35$, $p < 0.0001$, $\eta^2 = 0.64$) and accuracy ($F(2,57) = 3.48$, $p = 0.038$, $\eta^2 = 0.11$). There was no statistically significant effect for errors ($F(2,57) = 2.42$, $p = 0.098$, $\eta^2 = 0.08$) or SATO ($F(2,57) = 0.79$, $p = 0.459$, $\eta^2 = 0.03$). While SATO improved over the course of training, there was no significant group difference in gains scores. Thus, although a SATO occurs with practice, sleep does not preferentially enhance this trade-off, and therefore does not confound the interpretation of one or the other. Finally, it should be mentioned that there was no evidence of a ceiling or floor effect in

terms of reaching the maximum number of moves, or consistently performing the optional solution (**Supplemental Table S1**).

Follow-up independent samples t tests indicated that performance was significantly improved for Sleep vs. Wake for speed ($t(38) = 6.69$, $p < 0.0001$, $d = 2.12$) and accuracy ($t(38) = 2.08$, $p = 0.044$, $d = 0.66$), and Nap vs. Wake comparisons for speed ($t(38) = 8.86$, $p < 0.0001$, $d = 2.80$) and accuracy ($t(38) = 2.36$, $p = 0.024$, $d = 0.75$). Thus, either a full night of sleep or a nap afforded a benefit to task performance by increasing speed and accuracy from training to retest. It is worth noting that a nap afforded a greater benefit than a night of sleep for speed ($t(38) = 4.11$, $p < 0.001$, $d = 1.30$).

3.2. Polysomnographic Data. Descriptive statistics for sleep architecture variables for the experimental session in the Sleep and Nap conditions are reported in **Table 1**.

Table 1. Sleep architecture for experimental session. Means (M) and standard deviations (SD) are for time are displayed in minutes.

	Sleep Condition			Nap Condition		
	M	***SD***	**N**	**M**	***SD***	**N**
NREM1	17.23	*15.28*	20	5.63	*4.52*	20
NREM2	227.10	*34.73*	20	36.92	*12.76*	20
NREM3	74.90	*22.51*	20	21.09	*15.45*	19
REM	86.06	*23.86*	20	8.23	*4.79*	15
Wake After Sleep Onset	42.01	*30.11*	20	13.21	*12.85*	20
Total Sleep Time	405.29	*42.58*	20	68.79	*13.62*	20
Sleep Efficiency (%); (Time Asleep / Time in Bed)	87.59	*7.70*	20	77.97	*14.56*	20

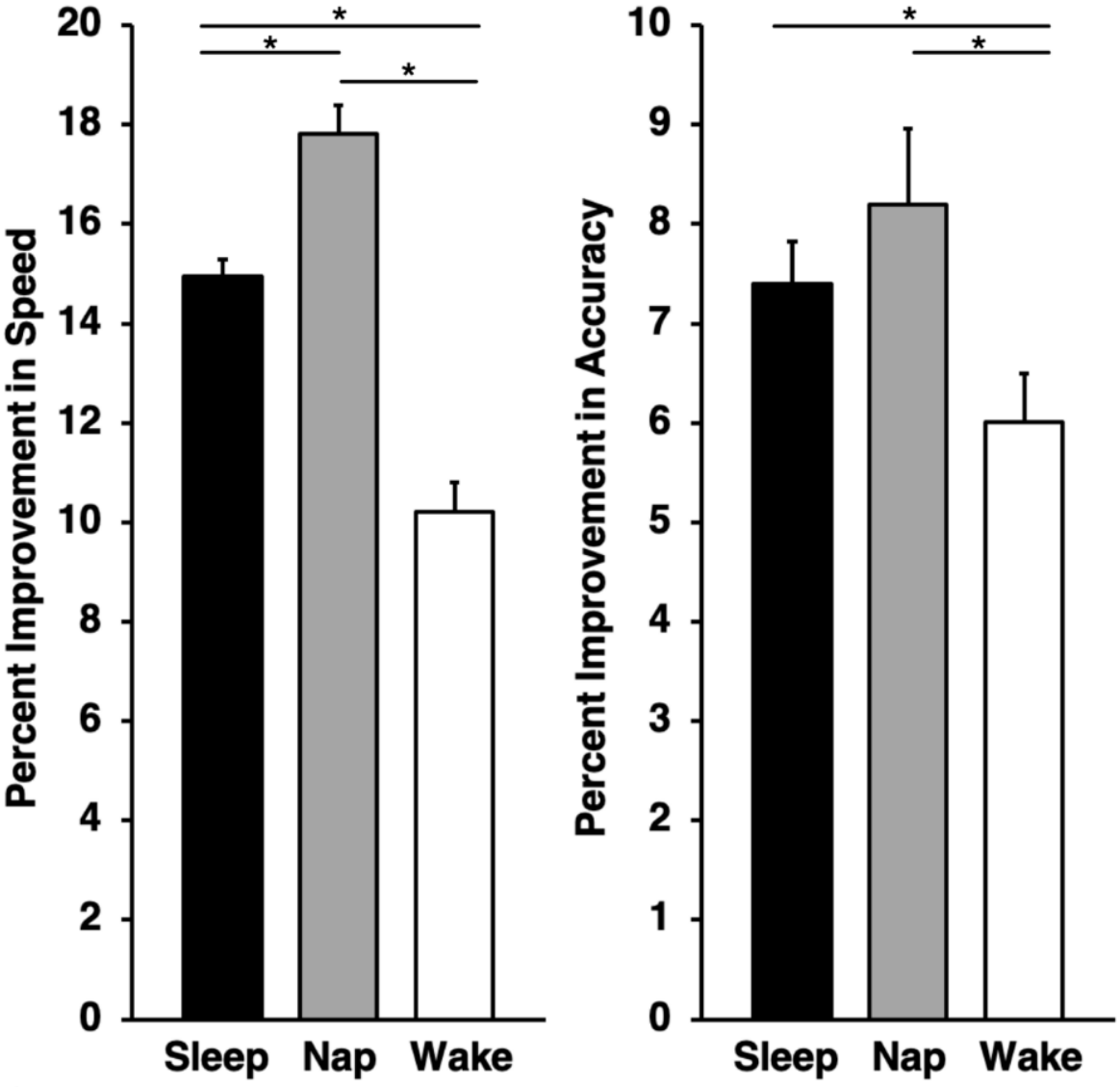

Figure 3. Offline gains in ToH performance (expressed as percent improvement in speed and accuracy) from Training to Retest for the Sleep, Nap and Wake groups. Error bars represent one standard error of the mean.

3.3. MRI Data: Retest > Training session

3.3.1. Sleep vs. Wake. As hypothesized, there was a significant group (Sleep vs. Wake) by session (Retest-Training) interaction in the anterior right hippocampus (Table 1) and a corresponding yet statistically non-significant difference (*i.e.,* significant only before whole-brain correction; $Z = 3.59$, $p < 0.001$, uncorrected) difference in the contralateral hippocampus.

More specifically, activation in the hippocampus was decreased in the Sleep group and increased in the Wake group. Further inspection of each participant's beta values and their relationship to behavioural performance are described below. It is worth noting that there was a similar pattern observed in the bilateral posterior hippocampus (*i.e.*, the parahippocampal gyrus), but only before whole-brain error correction ($Z = 3.55$, $p < 0.001$, uncorrected). In addition, increased activation was observed in the Sleep vs. the Wake group in the right caudate (**Figure 4**, **Table 2**).

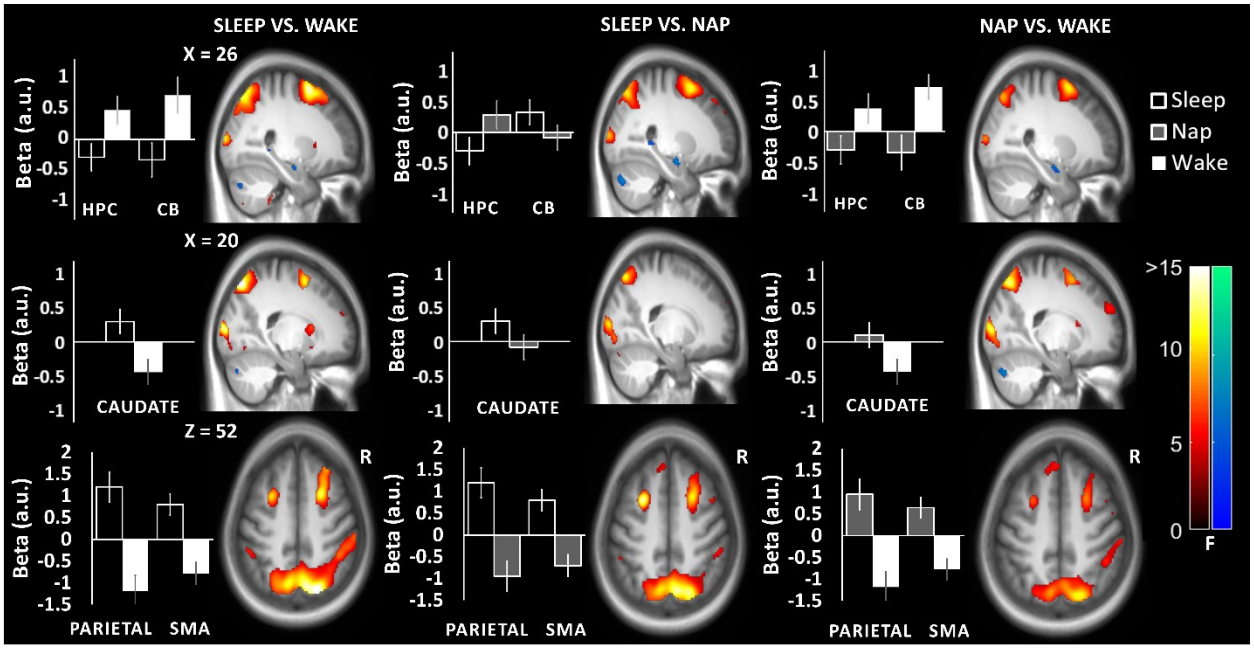

Figure 4. Significant brain activations in the Sleep *vs.* Wake, Sleep *vs.* Nap and Nap *vs.* Wake contrasts from training to retest. Changes in activation in the hippocampus and cerebellum (first row), the caudate (second row), and in the parietal and supplementary motor cortices (third row) are shown with corresponding contrast estimates (*beta* values in arbitrary units; *a.u.*) and 95% confidence intervals for the magnitude of the HRF. Warm colors reflect increases in activation and cool colors reflect decreases in activation. **Abbreviations:** Hippocampus (HPC); Cerebellum (CB); Supplementary Motor Area (SMA).

In addition to the hypothesized sleep-related changes in activation of the hippocampus and the caudate, there was a predictable group by session interaction in neocortical areas that support procedural skill learning, which were also recruited during training (**Supplemental Table S2**: training session). There was a widespread increase in activation in the Sleep condition

bilaterally in the SMA, which extended to the premotor cortex and inferior medial PFC. A bilateral increase in activation in the dorsolateral prefrontal cortex (dlPFC) was also observed. Another set of widespread activations was observed in the parietal and temporal cortex. Specifically, there was an extensive bilateral activation encompassing much of the dorsal ("where") visual stream in the Sleep vs. Wake condition, which was maximal in the superior parietal cortex, but extended ventrally into the inferior parietal and superior occipital cortex. In addition, there was also increased activation in the Sleep condition throughout much of the ventral ("what") visual stream, including the occipital cortex and posterior parietal cortex which extended to the precuneus, left angular gyrus, right supramarginal gyrus, and bilaterally throughout the temporal lobes to the temporal pole (**Supplemental Figure S2**). Finally, there was increased bilateral activation of the central cerebellar area and a decrease in cerebellar areas crus 1 and crus 2.

3.3.2. Sleep vs. Nap. Similar to the Sleep vs. Wake group comparison, decreased activation from training to retest was observed for the Sleep vs. Nap comparison bilaterally in the anterior hippocampus (**Figure 4**, **Table 2**). By contrast, no significant differences in the striatum (*e.g.*, caudate or putamen) were observed. A similar pattern of frontal cortical activation was observed in the Sleep vs. Wake comparison and was also observed in the Sleep vs. Nap comparison. Bilateral increases were observed in the SMA, premotor cortex, inferior medial PFC and left dlPFC. Widespread activations were also observed in the Sleep vs. Nap comparison in the occipital-temporal-parietal areas, again, in the same areas as the Sleep vs. Wake comparison. Widespread cortical activations in the inferior left occipital cortex, bilateral calcarine fissures, and lingual gyrus were also observed. There was also increased activation in areas crus 1 and crus 2 of the right cerebellum.

3.3.3. Nap vs. Wake. Similar to the Sleep vs. Wake comparison, bilateral decreased activation of the anterior hippocampus was also observed in the Nap vs. Wake comparison (**Figure 4**, **Table 2**). No enhancement of the striatum was observed, suggesting that a Nap may be sufficient to consolidate the trace in the hippocampus, but a night of sleep is required for observable changes to take place in the striatum. In terms of cortical areas, there was increased bilateral recruitment of the motor cortex, medial frontal and orbitofrontal area. Similar to the Sleep vs. Wake group comparison, the same widespread bilateral parietal and temporal increases in activation encompassing the dorsal and ventral visual streams were observed for the Nap vs. Wake comparison. Decreased activation was also observed in crus 1 and 2 of the cerebellum.

Table 2. Changes in activation from Training to Retest for, **A:** Sleep *vs.* Wake, **B:** Sleep *vs.* Nap, and **C:** Nap *vs.* Wake comparisons.

L/R	Level	Region	X	Y	Z	Size	Z	p FDR
		A: Sleep *vs.* Wake						
Bilateral	Cerebral Cortex	Superior & Inferior Parietal	10	-68	60	11979	>8.00	<0.001
Bilateral	Cerebral Cortex	Middle Temporal Gyrus	68	-40	0	2218	6.27	<0.001
Bilateral	Cerebral Cortex	Supplementary Motor Area	24	8	58	1982	7.35	<0.001
Bilateral	Cerebral Cortex	dlPFC	-48	36	28	498	5.91	<0.001
Bilateral	Cerebral Cortex	mPFC	2	20	46	289	4.64	0.012
Bilateral	Cerebral Cortex	Inferior Parietal	-52	-64	-8	169	4.98	0.005
Bilateral	Cerebral Cortex	Insula	32	24	2	446	5.99	<0.001
Right	Basal Ganglia	Caudate	20	16	10	446	4.76	0.009
Bilateral	Limbic	Hippocampus	24	-8	-18	90	4.65	0.012
Left	Hindbrain	Cerebellum	-30	-38	-44	322	4.78	0.008
Left	Hindbrain	Cerebellum	-6	-72	-52	41	4.65	0.012
Bilateral	Hindbrain	Cerebellum	-40	-68	-52	116	4.58	0.015
		B: Sleep *vs.* Nap						
Bilateral	Cerebral Cortex	Superior & Inferior Parietal	-12	-96	2	7605	7.77	<0.001
Bilateral	Cerebral Cortex	Middle Temporal Gyrus	66	-40	0	4489	6.78	<0.001
Bilateral	Cerebral Cortex	Supplementary Motor Area	26	10	58	809	6.39	<0.001
Bilateral	Cerebral Cortex	dlPFC	-10	50	42	388	4.72	0.017
Bilateral	Limbic	Hippocampus	-30	-12	-18	127	4.84	0.011
		C: Nap *vs.* Wake						
Bilateral	Cerebral Cortex	Superior & Inferior Parietal	8	-68	60	10116	7.70	<0.001
Bilateral	Cerebral Cortex	Middle Temporal Gyrus	-58	-32	-2	10116	6.52	<0.001
Bilateral	Cerebral Cortex	Supplementary Motor Area	24	10	56	4523	6.65	<0.001
Bilateral	Cerebral Cortex	Orbitofrontal Gyrus	-44	34	-10	1252	4.26	0.049
Bilateral	Limbic	Hippocampus	26	-6	-18	220	4.99	0.005
Right	Hindbrain	Cerebellum	24	-76	-34	224	5.24	0.002

Note: Results shown for significant activations at $p < 0.05$, corrected for multiple comparisons using whole-brain peak False Discovery Rate (FDR) correction. Maximum coordinate shown for bilateral activations. **Abbreviations:** dorsolateral prefrontal cortex (dlPFC); medial prefrontal cortex (mPFC); Left/Right (L/R)

3.4. Brain – Behaviour Relationships. Univariate General Linear Models tested whether the association between performance measures (speed, accuracy) and changes in brain activation (from training to retest) in selected and significant regions of interest (*e.g.*, hippocampus, caudate nucleus, supplementary motor area and prefrontal cortex) differed depending on (Sleep, Nap, Wake) condition. We did not explore any relationships with errors or SATO as they did not differ significantly among the 3 conditions.

These analyses confirmed that the relationship between performance improvements in speed and changes in brain activation differed among the 3 experimental conditions (see **Figure 5** for direction of change for each of the three groups). Significant changes were observed in the hippocampus (**Figure 5A**: $F(3,56) = 3.72$, $p = 0.017$), orbitofrontal cortex (**Figure 5B**: $F(3,56) = 3.92$, $p = 0.013$), precuneus (**Figure 5C**: $F(3,56) = 17.43$, $p < 0.001$), SMA (**Figure 5D**: $F(3,56) = 11.29$, $p < 0.001$), prefrontal cortex (**Figure 5E**: $F(3,56) = 4.77$, $p = 0.005$) and caudate nucleus (**Figure 5F**: $F(3,56) = 4.22$, $p = 0.009$). There were no significant brain-behaviour relationships for any brain regions for accuracy.

More specifically, in the hippocampus, a positive association between change in activation and speed-related performance improvements was observed in the Nap condition. In the Wake condition, the inverse relationship was observed (Nap vs. Wake: $t(36) = -2.94$, $p = 0.003$), and an intermediate relationship was observed in the Sleep condition (Sleep vs. Wake: $t(36) = -1.54$, $p = 0.066$). The Sleep condition was similar to the Nap condition (Sleep vs. Nap: $t(36) = 1.22$, $p = 0.116$). A very similar pattern was observed in the functionally and anatomically interconnected orbitofrontal cortex. In addition, the reverse overall pattern across groups was observed for the precuneus, SMA, prefrontal cortex and caudate nucleus. For these regions, the relationship between change in activation and performance improvements differed

between Sleep and the Wake condition (all p-values < 0.007), and the Nap and the Wake condition (all p-values < 0.001), but there was no difference between the Nap and the Sleep Condition (all p-values > 0.061).

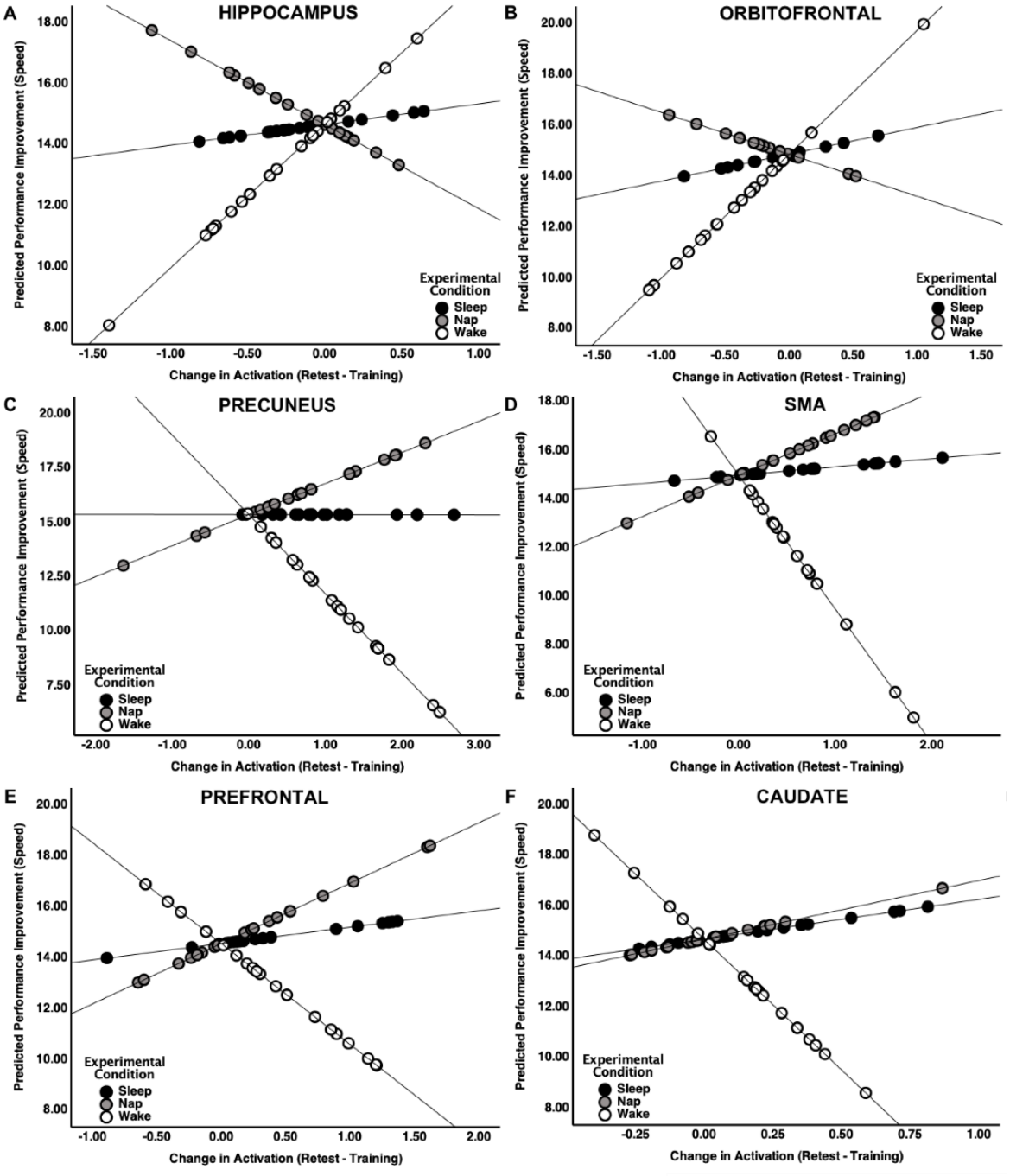

Figure 5. The relationship between the changes in performance (predicted values) and changes in brain activation from training to retest significantly differed across the three experimental conditions (Sleep, Nap, Wake). Predicted values displayed to show direction.

4. Discussion

The present study investigated how sleep affects the behavioural and functional brain changes upon awakening, which support novel problem solving. We subtracted BOLD activity that occurred during a motor execution control task from the BOLD activity that occurred during performance of the strategy-based ToH problem-solving task. Participants performed these two tasks in the fMRI before (i.e., "training" session) and after (*i.e.*, "retest" session) a period of sleep, nap, or wakefulness. Consistent with our hypotheses, we showed that from training to retest: 1) offline gains in task performance (*i.e.*, increased speed and accuracy) were greatest following sleep or a daytime nap, and, 2) the magnitude of the changes in brain activation for brain regions recruited during training depended on whether a night of sleep, a daytime nap, or a period of wakefulness occurred during the retention interval. Finally, 3) follow-up analyses of the brain-behaviour relationships show that for a given brain area, a dissociable relationship between changes in brain activation and offline improvements in performance depend on whether a consolidation interval contains overnight sleep, a daytime nap, or a period of wakefulness. Specifically, increases in brain activation from the training to the retest session were observed in the motor cortex, prefrontal cortex, as well as a widespread cluster of regions encompassing the dorsal and ventral visual stream, in all three comparisons (Sleep *vs.* Wake, Sleep *vs.* Nap, and Nap *vs*. Wake). Greater changes in hippocampal activation were observed from training to retest in Sleep *vs*. Wake, Sleep *vs*. Nap, and Nap *vs*. Wake comparisons. However, the caudate showed activation only in the Sleep vs. Wake comparison. Overall, these results suggest that: 1) either a nap or a full night of sleep benefits performance in terms of speed and accuracy, and, 2) a full night of sleep is required for optimal neural enhancement (*i.e.*, greater changes in the hippocampus, and for changes to occur in the caudate) for a newly acquired strategy necessary for problem-solving skills.

The striatum plays a key role in both motor learning and strategy learning; however, the subregions of the striatum (*e.g.*, putamen and caudate) are specialized to support these distinct functions, respectively (Liljeholm & O'Doherty, 2012). Specifically, the putamen is involved in reinforcement-based reward learning, conditioning and motor sequence learning (Lansink et al., 2009; 2016; Pennartz et al., 2004; Liljeholm & O'Doherty, 2012), whereas the caudate supports higher-order reasoning, novel learning (*e.g.*, strategies) and problem-solving skills (Doyon et al., 1996; Dagher et al., 1999; Grafton, Hazeltine, & Ivry 2002; van den Heuvel et al., 2003; Monchi et al., 2006; Unterrainer & Owen 2006; Pezzulo et al., 2014). It is well-established that the putamen is implicated in sleep-related consolidation of motor sequences (Debas et al., 2010; Barakat et al., 2013; Fogel et al., 2014; 2017; Boutin et al., 2018). However, much less is known about the role sleep for the consolidation of problem-solving skills (which also involve motor sequence learning), and whether an analogous process occurs, specifically in the caudate. As predicted, sleep as compared to an equivalent period of wake showed increased activation in the caudate, but not in the putamen. A daytime nap was not sufficient to afford this benefit. Interestingly, and importantly, hippocampal activation was reduced in the Sleep vs. Wake and the Nap vs. Wake comparisons, suggesting that either a full night of sleep or a nap can facilitate the hippocampal-neocortical dialogue that is involved in memory consolidation. In addition, the significant difference in the Sleep vs. Nap condition for the hippocampus (and other brain areas) suggests that there is an additional transformation of the memory trace over a night of sleep over-and-above a daytime nap. While the behavioural benefit of Sleep vs. Wake also manifested after a daytime nap, sleep appears to continue to be involved in longer-term transformation of the memory trace, which may afford benefits not investigated here (*e.g.*, resistance to forgetting or interference, generalization, integration, schematization, etc.). However, this possibility remains

to be investigated. Overall, these results suggest that a full night of sleep is required for optimal neural enhancement for a newly acquired strategy necessary for problem-solving skills. In addition, while a nap might be sufficient for the faster processes which involve the hippocampus, a slower consolidation process involving the caudate requires a whole night of sleep. This finding is consistent with accounts (*e.g.*, Walker & Stickgold, 2010) suggesting that dissociable aspects of memory consolidation (*e.g.*, strengthening and integration) during sleep occur sequentially in distinct sleep stages (SWS & REM sleep), and possibly within or across several nights (Lehericy et al., 2005; Conte & Ficca, 2013). While the specific role of different sleep stages remains to be investigated, our results suggest that these dissociable processes might involve dissociable brain areas (*e.g.*, hippocampus and striatum).

Interestingly, while cortical and caudal activations increased after sleep (as compared to wake), recruitment of the hippocampus was decreased after sleep. This observation is consistent with the classical (albeit sometimes contentious) view that the hippocampus is a temporary waystation for newly acquired information before transferring it to the cortex for long-term storage (Dudai, 1996; Squire & Zola-Morgan, 1996; Dudai, Karni, & Born, 2015), but see (Nadel & Moscovitch, 2001; Rosenbaum, Winocur, & Moscovitch, 2001; Schapiro et al., 2019) for alternate and complementary views. It is thus possible that the memory trace following wake was still labile in the hippocampus, whereas following sleep or a nap, consolidation was accelerated, as reflected by reduced hippocampal recruitment at retest.

In addition to sleep-related changes in the hippocampus and caudate, there was a strong bilateral activation that was maximal in the superior parietal cortex extending into the inferior parietal and superior occipital cortex. This extensive activation was greatest in the Sleep condition, and encompassed much of the dorsal (*i.e.*, “where”) visual stream, which is involved

in processing spatial information, the guidance of actions and recognizing where objects are in space. There was also a similarly widespread activation that was greatest in the Sleep condition throughout much of the ventral ("what") visual stream, including the occipital and posterior parietal cortices, which extended bilaterally throughout the temporal lobes. These widespread activations are in line with PET and fMRI studies employing the ToH and similar tasks (Baker et al., 1996; Owen et al., 1996; Lazeron et al., 2000). This is not surprising given the nature of the task, which requires the movement of objects of different colours and sizes that can be demanding on visual associative areas (Corbetta et al., 1991) and requires these objects to be moved from one spatial location to another as determined by higher-order processing and planning. In addition, changes in activation in the prefrontal cortex (Sleep vs. Wake) and orbitofrontal gyrus (Nap vs. Wake) were observed - brain regions typically involved in planning, problem solving and goal-directed spatial memory. It is worth noting that the orbitofrontal cortex is implicated in error inhibition (Elliott & Deakin, 2005; Stevens et al., 2009), receives projections from the caudate (Haber, Kunishio, & Mizobuchi, 1995), and is functionally interconnected with the hippocampus which performs complementary functions (Wikenheiser & Schoenbaum. 2016). Areas including the SMA and prefrontal cortex (Aron, Robbins, and Poldrack, 2004; Lehéricy et al., 2005; Cieslik et al., 2015) are implicated in planning, error processing and performance monitoring. The greatest changes in these areas were observed following a period of sleep.

Finally, we investigated the relationship between performance improvements and changes in brain activation across the 3 conditions. The greater the reduction of hippocampal and orbitofrontal activation, and related brain areas such as the medial prefrontal cortex, the better the performance improvements in the Nap condition. The inverse relationship was observed in

the Wake condition, and an intermediate association was observed in the Sleep condition. By contrast, the reverse overall pattern across conditions was observed for the precuneus, SMA, prefrontal cortex and caudate nucleus. Specifically, changes in brain activation from training to retest in these brain areas was positively associated with improved performance in both the Sleep and Nap conditions, whereas a negative association was observed in the Wake condition. Taken together, these results suggest that sleep-dependent changes in brain activation which support the acquisition of novel cognitive strategies required for problem solving are associated with sleep-related changes in performance. The pattern of these relationships is consistent with the notion that the greater the decrease in recruitment in the hippocampus and related brain regions (*e.g.*, orbitofrontal cortex), the greater the performance improvements. The opposite pattern was observed in motor cortical areas involved in planning (*e.g.*, SMA), whereby greater increases in activation following sleep were related to improved performance.

Many of the relationships between performance enhancements and changes in brain activation were also apparent in the Nap condition, which may explain why robust changes in performance improvements are also observed after a daytime nap. However, it is important to note that the brain-behaviour associations in the Wake condition are in all cases distinct from both the Sleep and the Nap condition (except for the hippocampus and orbitofrontal cortex, which were only statistical trends when comparing the difference in the association between changes in brain activation and performance improvements in Sleep vs. Wake, directly).

In summary, both a daytime nap and a night of sleep can contribute to problem solving relative to wake, however, a full night of sleep is optimal – and perhaps necessary – for the process to be fully realized in terms of both the neuronal and behavioural manifestations.

4.1. Implications and Future Directions. Several questions remain unresolved. It is not conclusive how much sleep is sufficient for optimal consolidation. There is evidence that even a brief nap (*i.e.*, 20 minutes or less) can benefit memory when compared to a period of wake (Lahl et al., 2008). Fewer errors have been associated with higher-order procedural memory consolidation following a night of sleep, but not following a nap (van Schalkwijk et al., 2019). Some studies report that a daytime nap can afford the same or similar benefit as a night of sleep (Doyon et al., 2009; Albouy et al., 2013). However, conflicting evidence suggests that naps might merely stabilize procedural skills (Tucker et al., 2006; Sugawara et al., 2018; van Schalkwijk et al., 2019). Several factors might explain these inconsistencies. For example, inherent differences between nocturnal sleep and daytime naps (*e.g.*, varying length, architecture, sleep quality, circadian influences, sleep pressure) preclude clear and direct comparisons. However, some comparisons can still be made, particularly in examining the characteristics of sleep architecture. For example, the presence or absence of REM sleep during a daytime nap appears to be a key predictor of post-napping problem solving (Tucker et al., 2006) or perceptual learning (McDevitt et al., 2015). Moreover, the degree of improvement is proportional to the amount of REM sleep (McDevitt et al., 2015), providing some evidence for a dose-response relationship. Similarly, other findings suggest that "a nap is as good as a night" for visual texture discrimination memory, but only if the nap contains REM sleep (Mednick, Nakayama, & Stickgold, 2003). The presence or relative absence of REM sleep during a nap might explain differences in memory consolidation as compared to a full night of sleep.

Finally, it is also not known which neural/electrophysiological mechanisms might support this process. Simultaneous EEG-fMRI sleep studies can further clarify how sleep-related neural oscillations might influence the neuroanatomical changes that occur during sleep.

Reactivation studies have shown that the brain regions which are active during learning, are also reactivated during post-learning sleep (Maquet et al., 2000; Fogel et al., 2017; Boutin et al., 2018). Specifically, following sequence learning, activation of the putamen time-locked to spindles was associated with improved performance (Fogel et al., 2017). It is possible that an analogous process occurs for strategy and problem-solving skills. Simultaneous EEG-fMRI studies can provide a more complete understanding of how sleep supports the realization of complex strategies needed for problem solving.

5. Conclusion

A night of sleep affords a benefit to the consolidation of the striatal (*e.g.*, caudate), hippocampal, prefrontal and motor cortical and related aspects (*e.g.*, SMA, cerebellum) of problem-solving skills. However, if only a daytime nap occurs during the retention interval, these sleep-dependent changes in brain activation are apparent in some areas (*e.g.*, hippocampus and the SMA), but not in the striatum. Thus, to get the full benefit of sleep, a full night of sleep is required. Distinct contributions of the hippocampus and putamen have been observed for learning and sleep-related consolidation of motor sequences (Albouy et al., 2008; Albouy, Sterpenich, et al., 2013). Here, our results suggest that an analogous process may take place for sequences of movements that also involve problem-solving skills, but in brain regions specialized for this task, including the caudate, rather than the putamen. This strengthening of activation in the caudate required a full night of sleep. Moreover, the involvement of the hippocampus as the consolidation process unfolds, as observed here, is consistent with the notion that the hippocampus is important for early stages of the consolidation process but is less involved after a period of sleep. Thus, sleep facilitates the realization of a novel cognitive strategy, perhaps through two distinct processes: a rapid consolidation-based hippocampal-neocortical transfer of information, and a slower consolidation process in the striatum. Sleep may

be an opportune time to actively facilitate the transfer of information to other brain areas for more permanent storage.

The processes by which we gain insight and inspiration into the solution to a problem is not well understood, nor is the putative contribution of sleep, or the underlying neuronal processes. Sleep appears to have a privileged role in facilitating novel cognitive strategy learning. This study suggests that sleep facilitates and enhances the transformation of the neuronal activity that supports ingenuity, and ultimately, novel discoveries.

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Supplemental Material

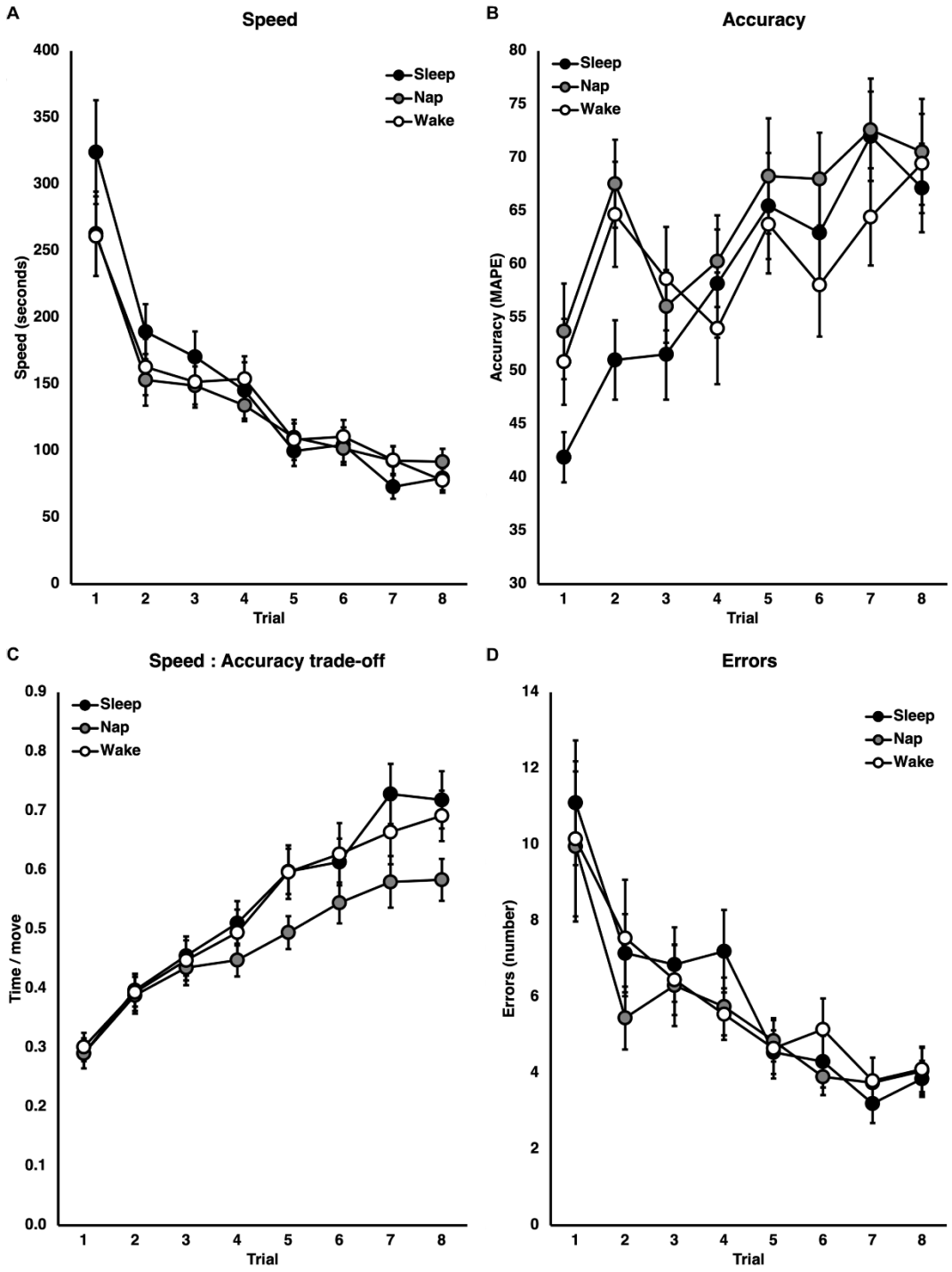

Figure S1. Time course of behavioural performance during each training trial, for (**A**) Speed, (**B**) Accuracy, (C) Speed:Accuracy Trade-Off, and (**D**) Errors.

Table S1. Percent of trials where the maximum number of moves (93 moves) was reached and percent of trials where the optimal solution was executed (31 moves) at training and retest for the Sleep, Nap and Wake conditions.

	% trials exceeding max # of moves (93 moves)				% of trials executing perfect solution (31 moves)			
	Training		Retest		Training		Retest	
	M	SD	M	SD	M	SD	M	SD
Sleep	0.00	0.00	0.00	0.00	8.75	19.41	18.75	31.50
Nap	0.63	2.72	0.00	0.00	10.00	18.79	21.25	33.80
Wake	1.25	3.75	1.25	5.45	8.75	17.28	18.75	33.42

Table S2. Performance-related activations during ToH training session for all participants, after controlling for motor movements (ToH-CTL).

L/R	Level	Region	X	Y	Z	Size	Z	p FDR
Bilateral	Cerebral Cortex	Superior & Inferior Parietal	8	-66	54	18887	>6.50	<0.001
Bilateral	Cerebral Cortex	Premotor	-24	2	62	801	>6.50	<0.001
Bilateral	Cerebral Cortex	dlPFC	-48	30	30	749	6.50	<0.001
Bilateral	Cerebral Cortex	mPFC	-10	34	52	3644	5.41	0.001
Bilateral	Cerebral Cortex	Inferior Frontal	50	22	14	1329	5.09	0.002
Bilateral	Cerebral Cortex	Middle Temporal Gyrus	66	-34	-2	2846	>6.50	<0.001
Bilateral	Cerebral Cortex	Inferior Temporal	54	-6	-34	473	5.47	<0.001
Left	Limbic	Anterior Cingulate	-18	32	-2	150	4.59	0.014
Bilateral	Hindbrain	Cerebellum Crus 2	-26	-82	-36	236	5.34	0.001
Bilateral	Hindbrain	Cerebellum	-32	-38	-42	685	5.25	0.001

Note: Results shown for significant activations at $p < 0.05$, corrected for False Discovery Rate (FDR). Maximum coordinate shown for bilateral activations. **Abbreviations:** medial prefrontal cortex (mPFC); dorsolateral prefrontal cortex (dlPFC)

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Chapter 4: Study 3

Sleep strengthens resting-state functional communication between brain areas involved in the consolidation of problem-solving skills

Abstract

Sleep consolidates procedural memory for motor skills, and this process is associated with strengthened functional connectivity in hippocampal-striatal-cortical areas. It is unknown whether similar processes occur for procedural memory that requires cognitive strategies needed for problem solving. It is also unclear whether a full night of sleep is indeed necessary for consolidation to occur, compared to a daytime nap. We examine how resting-state functional connectivity within the hippocampal-striatal-cortical network differs after offline consolidation intervals of sleep, nap, or wake. Resting-state fMRI data was acquired immediately before and after training on a procedural problem-solving task that requires the acquisition of a novel cognitive strategy, and immediately prior to the retest period (i.e., following the consolidation interval). ROI-to-ROI and seed-to-whole-brain functional connectivity analyses both specifically and consistently demonstrated strengthened hippocampal-prefrontal functional connectivity following a period of sleep vs. wake. These results were associated with task-related gains in behavioural performance. Changes in functional communication were also observed between groups using the striatum as a seed. Here, we demonstrate that at the behavioural level, procedural strategies benefit from both a nap and a night of sleep. However, a full night of sleep is associated with enhanced functional communication between regions that support problem-solving skills.

Keywords: sleep, memory consolidation, procedural memory, strategy learning, resting-state connectivity, functional connectivity

1. Introduction

Proficiency at solving cognitively complex procedural problems does not materialize instantly. Rather, this type of skill learning develops gradually, usually requiring trial-and-error, repeated practice, and for optimal performance, an offline consolidation period of sleep (Fogel et al., 2015). Sleep is indeed known to facilitate creativity and to act as a cognitive catalyst for realizing solutions to cognitively complex problems (Wagner et al., 2004; Sio et al., 2013; Monaghan et al., 2015). Sleep is known to preferentially consolidate this type of memory over-and-above memory for the simple motor movements typically required to execute the solution (Van Hedger et al., 2015; van den Berg et al., 2019; Conte et al., 2020).

Functional Magnetic Resonance Imaging (fMRI) techniques can further elucidate how the sleeping brain actively consolidates newly formed memory traces. For example, sleep enhances consolidation of procedural memory traces for motor skills (Debas et al., 2010; Albouy et al., 2013c). Brain areas such as the striatum, hippocampus, motor cortex and prefrontal cortex are recruited during learning. They exhibit subsequent sleep-dependent changes in activity, and these changes are associated with offline gains in performance (Debas et al., 2010; Albouy et al., 2013c).

Specifically, striatal activity in both the putamen (Albouy et al., 2013c; Barakat et al., 2013; Boutin et al., 2018) and the caudate (Cousins et al., 2016; van den Berg et al., 2021) is associated with sleep-related consolidation of procedural memories. During sleep itself, the putamen is reactivated when sleep spindles occur. Sleep spindle characteristics and the extent of this reactivation are both associated with improved motor sequence memory performance upon awakening (Fogel et al., 2017). In addition, in part because of recent findings from sleep studies, the hippocampus is becoming increasingly recognized as a central hub for procedural memory consolidation (Schendan et al., 2003; Albouy et al., 2013a; Albouy et al., 2013b; Sawangjit et al.,

2018; Schapiro et al., 2019). Sleep-related consolidation of simple motor sequences (Fogel et al., 2014), and of procedural problem-solving skills involving cognitive strategies (van den Berg et al., 2021), are both associated with increased hippocampal activity compared to an equivalent period of wake.

Importantly, these brain areas (*i.e.*, the hippocampus and striatum) do not act in isolation when memory consolidation occurs, and they each have functionally distinct roles as the consolidation process unfolds over a period of sleep. Specifically, a competitive interaction exists between the hippocampus and striatum during learning and consolidation periods of simple motor sequences (Albouy et al., 2008, 2013c). The hippocampus is involved in consolidation of the spatial aspect and is sleep-dependent (Albouy et al., 2013a; 2015). The striatum (*i.e.,* the putamen) is involved in consolidating the motor aspect, and although it does so regardless of sleep or wake (Albouy et al., 2013a), a period of sleep can modulate its involvement through interactions with the hippocampus (Albouy et al., 2013b). In addition, the strength of reactivation of the putamen at night correlates with the magnitude of offline gains in motor sequence performance (Fogel et al., 2017). Most recently, we identified an analogous process for the hippocampus and the caudate for procedural skills that involve the acquisition of novel cognitive strategies necessary for problem solving. Specifically, activation of the caudate increased after a period of sleep (*vs*. wake), whereas activation of the hippocampus decreased (van den Berg et al., 2021). Thus, depending on the exact nature of the memory type, dissociable domain-specific areas (*i.e.,* putamen, or the caudate) interact with the hippocampus over the course of sleep-dependent memory consolidation. One of the aims of the current study is to determine if a similar functional dissociation is observed for sleep-related changes in hippocampal-striatal functional connectivity over the course of the consolidation of novel

cognitive strategies, when comparing retention intervals of nocturnal sleep, a daytime nap, or daytime wakefulness.

Prefrontal cortical areas are also thought to interact with hippocampal and striatal areas (Albouy et al., 2013b). The orbitofrontal cortex (OFC) in particular interacts with the hippocampus when performing cognitively demanding skills (Wikenheiser & Schoenbaum, 2016), specifically, when encoding memories that involve reward-learning (Knudsen et al., 2020), trial-and-error learning (Hornak et al., 2002), and goal-directed strategy switching (Young and Shapiro 2011). Functional connectivity between these two areas is also thought to optimize complex and abstract reinforcement learning, even in the absence of direct physical cues (Wang et al., 2020). Similarly, the striatum and OFC are thought to work cooperatively; indeed, they are structurally connected to one another (Haber et al., 1995). Excision of either the OFC or the dorsolateral prefrontal cortex (dlPFC) impairs trial-and-error reinforcement learning (Hornak et al., 2002), and the dlPFC is recruited alongside both the hippocampus and striatum during the insight moment of creative problem solving (Tik et al., 2018). Together, these studies support the developing hypothesis that the hippocampus and striatum interact, possibly via the prefrontal cortex, to consolidate procedural memories (Albouy et al., 2013b). The caudate and the prefrontal cortex might be especially important for the consolidation of procedural memories involving complex problem-solving skills, however more research is required to support this speculation.

Given these complex interactions between brain areas, resting-state functional connectivity approaches provide a useful way to assess systems-level memory consolidation. Assessing the functional connectivity among these brain regions has further revealed the transformation process that occurs over the course of sleep-dependent memory consolidation

(Vahdat et al., 2017; Fang et al., 2021; Samanta et al., 2021). For example, taking a short daytime nap (as compared to remaining awake) after learning a novel motor procedural skill enhances both offline gains in performance, and the functional connectivity between the putamen and motor cortical areas (Fang et al., 2021). In addition, simultaneous EEG-fMRI sleep recording studies have shown that functional connectivity increases only during periods of NREM sleep, but not wake, in subcortical areas involved in the consolidation of procedural memories (Vahdat et al., 2017). Moreover, the putamen was found to be a central hub for this increased connectivity that occurred exclusively during post-learning sleep, and the strength of this connectivity was related to offline gains in performance (Vahdat et al., 2017). Thus, changes in functional connectivity can provide insight into how sleep is involved in the enhancement and reorganization process that supports systems-level memory consolidation.

Our understanding of the alterations of functional connectivity that reflect sleep-related procedural memory consolidation is currently limited to cognitively simple motor skills. Importantly, task complexity moderates the benefit of sleep for procedural memory consolidation (Kuriyama et al., 2004; Blischke & Malangré 2017), and sleep preferentially enhances memory for cognitive strategies over-and-above the motor skills needed to acquire them (Van Hedger et al., 2015; van den Berg et al., 2019; Conte et al., 2020). At the neural level, sleep-related consolidation of procedural problem-solving skills is associated with changes in brain areas involved in both motor skills (*e.g*., motor cortex, cerebellum) and areas involved in higher-order cognitive skills (*e.g*., caudate, hippocampus and prefrontal cortex; van den Berg et al., 2021). However, it is not known how a period of sleep *vs*. wake may impact the evolution of functional connectivity over the course of the consolidation of novel cognitive strategies that are involved in problem solving. Nor is it known whether such sleep-related changes in functional

connectivity might be correlated with the extent of offline improvements in performance. Examining functional connectivity, specifically in these hippocampal-striatal-cortical areas, can provide valuable insight into the processes that enhance memory consolidation which unfold preferentially over the course of sleep.

Finally, it is not clear how much sleep is needed for optimal memory consolidation to occur. Some studies suggest that a nap is as good as a night of sleep for consolidating memory (Mednick et al., 2003; Doyon et al., 2009). Our recent work has shown that a consolidation interval containing either a full night of sleep, or a 90-minute daytime nap does benefit problem-solving skills. However, at the neural systems level, task-related cerebral activation of critical areas was greatest following a full night of sleep (van den Berg et al., 2021). It remains to-be-investigated whether changes in resting-state functional connectivity might elucidate the unique benefits of a nap *vs*. a night of sleep for memory consolidation.

Resting-state functional connectivity analysis allows for an exploration of the functional relationship between time series of brain areas, even if the brain areas are not structurally adjacent. Here, we examined changes in resting-state functional connectivity following a consolidation interval of either a sleep, nap, or equivalent period of wakefulness among brain areas required for problem-solving skills. Regions of interest (ROIs) that showed sleep-related, task-specific activation from the same experiment (van den Berg et al., 2021), as well as a similar study employing motor sequence learning (Vahdat et al., 2017) were used as seed regions for the fMRI analyses in the present study.

Specifically, we examined: **1)** how sleep impacts memory consolidation for a novel problem-solving skill, **2)** how functional communication between the hippocampus, striatum (*i.e.*, caudate, putamen), motor cortex, and prefrontal cortex (*i.e.,* OFC, dlPFC) evolves after

acquiring a novel cognitive procedural strategy, **3)** if changes in functional connectivity between these ROIs differ depending on whether a night of sleep, or a daytime nap compared to a day of wakefulness occurs during the consolidation interval, and, **4)** whether the changes in functional connectivity are correlated with offline gains in performance for problem-solving skills in Sleep *vs*. Nap *vs*. Wake groups.

2. Methods

2.1. Participants. The data analyzed in this study were part of a larger polysomnographic, behavioural, and MRI protocol employing various techniques intended to address a variety of research questions. The resting-state fMRI data have not been reported elsewhere, and are unique to this study. See van den Berg et al. (2021) for additional details about the experimental protocol, specific to that study. All methods relevant to the current investigation are reported here. Participants were between 20 and 35 years of age, right-handed with no hand/finger mobility issues, were non-shift workers, took no medications known to interfere with sleep, and had consistent sleep schedules (*i.e.,* 7-10 hours of sleep, a bedtime between 2200 and 0100, and wake time before 0900). Participants had a body mass index (BMI) < 30, had normal or corrected-to-normal vision, considered themselves a "non-smoker", consumed less than 2 caffeinated drinks per day, and consumed limited alcohol (*i.e.,* <7 drinks/week). Participants were excluded if they considered themselves a poor sleeper, had a history of chronic pain, seizures, or head injury, or had familiarity with the Tower of Hanoi (ToH) task. Furthermore, participants scored <10 on the Beck Anxiety (Beck et al., 1988) and Beck Depression (Beck & Beamesderfer, 1974) Inventories, and had no signs of sleep disorders as determined by the Sleep Disorders Questionnaire (Douglass et al., 1994).

Participants who met the above criteria underwent an overnight polysomnography (PSG) night to screen for sleep disorders, which took place one week before the experimental sessions.

Participants were excluded if their screening night sleep efficiency was <85%, if they had >5 respiratory events/hour (indicating signs of sleep apnea) or showed indications of parasomnias. This PSG night also served to acclimatize participants to the sleeping environment. Finally, all participants wore a Motionlogger actigraph (a wrist-worn accelerometer; Ambulatory Monitoring Inc., Ardsley, NY, U.S.A.), and were asked to complete a log of their sleep/wake habits for the duration of the study to verify compliance with the study protocol.

Power analyses determined the required sample size for observing both behavioural effects and MRI effects. Using alpha set to 0.05 to obtain 80% power, based on an effect size of $f = 0.9$ for behavioural effects, and a more conservative $f = 0.7$ for MRI effects, we would require a minimum of n=15 per group. To ensure adequate power for all analyses, we aimed to have final sample sizes of $n = 20$ per group. Four participants were excluded from the study for non-compliance with the experimental protocol based on the results of their actigraph and sleep/wake log. One participant voluntarily dropped out of the study following the PSG screening night. The final sample of 60 healthy young adults (34 females; aged 20-35 years; $M_{age} = 24.38$, SD = 4.44) were randomly assigned to either the sleep (Sleep; $n = 20$), nap (Nap; $n = 20$), or wake (Wake; $n = 20$) groups.

2.2. Ethics statement. All study procedures were approved by the Research Ethics Boards at the University of Ottawa and The Royal's Institute of Mental Health Research (IMHR). All participants provided written informed consent prior to participation and were financially compensated for their participation.

2.3. Experimental protocol. Following the PSG screening night, eligible participants returned to the lab for the experimental session one week later (see **Figure 1** for the study design). Upon arrival to the lab, participants completed the training session by performing 8

trials of the ToH task. The training session was flanked by 8-minute resting-state scans ("Rest 1" and "Rest 2"), immediately before and after the training session. This was followed by either: 1) an overnight PSG sleep recording (Sleep group), 2) a 90-minute daytime PSG recording (Nap group), or, 3) a daytime wake period (Wake group). Following these intervals (and after a >30-minute wake period to allow the effects of sleep inertia to dissipate in the Sleep and Nap groups), all participants completed the retest session. The retest session involved performing 4 trials of the ToH, and was immediately preceded by an 8-minute resting-state scan ("Rest 3"). For all resting-state scans, participants were instructed to stay relaxed, keep their eyes open and keep their gaze fixed on an on-screen plus sign ('+').

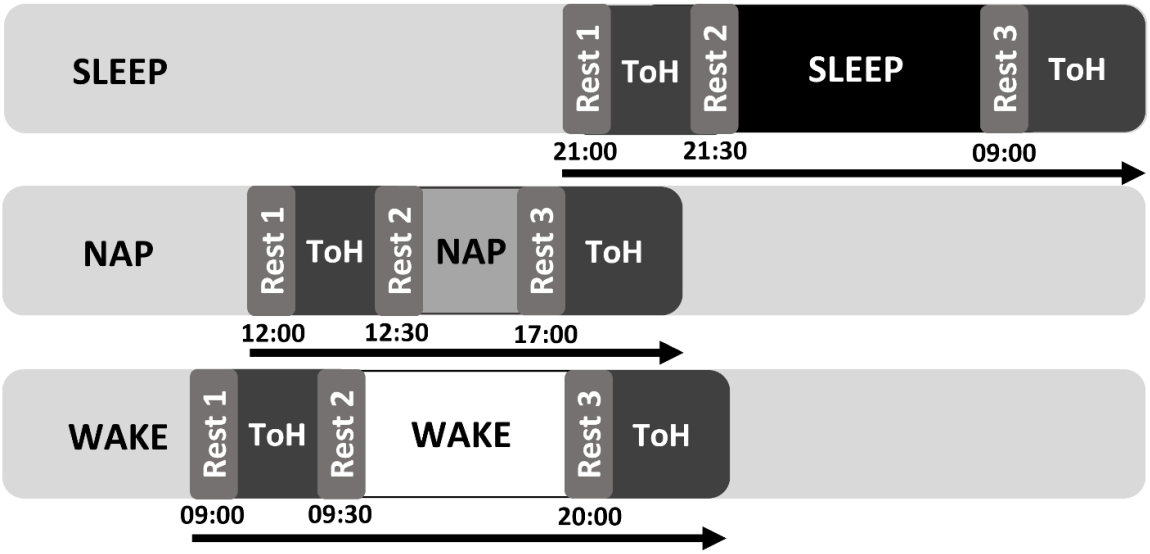

Figure 1. Study design. Following a screening and acclimatization night of PSG, participants returned one week later to the laboratory for the experimental session. N=20/group were assigned to either the *Sleep*, *Nap* or *Wake* group, and underwent MRI imaging sessions to obtain resting-state fMRI BOLD images before training (*Rest 1*), after training (*Rest 2*), and after the retention interval, but prior to retest (*Rest 3*). In the **Sleep group**, Rest 1 began at ~2100 h, and Rest 2 began 20-30 mins later (at ~2130 h). The 8-hour sleep opportunity began at ~2200h and Rest 3 began 10-11 hours later (~0900 h). In the **Nap group**, Rest 1 began at ~1200 h, and Rest 2 began 20-30 mins later (at ~1230 h). The 90-minute sleep opportunity began at ~1400 h and Rest 3 began 3 hours later (~1700 h). In the **Wake group**, Rest 1 began at ~0900 h, Rest 2 began 20-30 mins later (at ~0930 h), and Rest 3 began 10-11 hours later (~2000 h). It is important to note that the intervals between sleep and wake were held constant. Participants in the Wake group remained awake in between the training and retest sessions (confirmed via actigraphy).

2.4. Behavioural task and analysis

2.4.1. Tower of Hanoi. The ToH task was coded in MATLAB R2016a (Mathworks Inc., Natick, MA, USA) using the Psychophysics Toolbox extension v3.0.12 (Brainard 1997; Kleiner et al., 2007) for Windows (Microsoft, Redmond, WA, USA). The start configuration of the task included three identical, equally-spaced pegs, with 5 disks stacked on the far-left peg in ascending order of size (*i.e.*, largest disk on the bottom, smallest disk on the top). The ToH requires the participant to acquire a novel cognitive strategy (*i.e.,* the use of recursive logic) to solve the problem in the minimum number of moves. There is only one optimal solution to the puzzle, which can be learned through trial-and-error.

Participants were instructed that, for each trial, the objective of the task was to transfer all disks from the initial position on the far-left peg to the final position on the far-right peg in the same ascending order. They were instructed that this was to be accomplished under the following constraints: (1) only one disk could be moved at a time, (2) only the upper-most disk from any one of the three pegs could be selected, and, (3) a disk could only be placed on an empty peg or on another disk that is larger in size. Participants could control the on-screen movement of the disks with an MR-compatible fibre optic button pad (model HHSC-2x4-C; Current Designs Inc., Philadelphia PA, USA) using one of three push buttons equally spaced apart in a horizontal row. Participants were instructed to perform the task as quickly and accurately as possible, with their right hand, where their index, middle, and ring fingers respectively corresponded to the first (*i.e.*, far-left peg), second (*i.e*., middle peg) and third (*i.e*., far-right peg) buttons. The buttons controlled the movement of the disks '*from*' and '*to*' one of the three pegs. A trial ended when all five disks were in ascending order on the far-right peg, or if the maximum number of moves was reached before successful completion of the task. The maximum number of moves for the 5-

disk task was set at 93 (*i.e.*, three times the optimal number of moves $2^N - 1$, where N is the number of disks; $2^5 - 1 = 31$). Every trial of the ToH task was followed by a 20-second rest period during which the three ToH pegs were still visible, but with no disks. Participants were instructed to abstain from pressing any buttons during this time.

The variables of interest for the ToH task were speed (*i.e.*, time to complete each ToH trial), accuracy (Mean Absolute Percentage Error; MAPE) and speed-accuracy trade-off (SATO). The MAPE can be interpreted as a percentage of perfect performance (*e.g.*, 100% reflects perfect performance, whereas 50% reflects making twice as many errors as perfect performance, and 0% represents an infinite number of moves). The % improvement for all variables was calculated by taking the performance in the retest trials minus performance in the training trials, divided by performance in the training trials, multiplied by 100:

$$\%\ \text{improvement} = \left(\frac{\text{Retest} - \text{Training}}{\text{Training}}\right) * 100$$

2.4.2. Behavioural analysis. All behavioural statistical analyses were carried out using SPSS Statistics version 25 (IBM, Armonk, New York, U.S.). To ensure that task acquisition (*i.e.,* learning) occurred during the training session, a block by trial ANOVA was performed across all participants. Next, ToH performance improvement across the interval of sleep, nap, or wake was measured using three separate one-way ANOVAs for measures of speed, accuracy and SATO. Significant effects were followed-up with planned comparison *t*-tests.

2.5. Polysomnographic recording and analysis

2.5.1. Polysomnographic recording parameters and analysis. Polysomnography **(**PSG) was recorded with the Embla N7000 32-channel amplifier system (Natus, Pleasonton, CA, USA) sampled at 500 Hz. Scalp-recorded EEG from 13 channels (Fp1, Fp2, Fpz, F3, F4, Fz, C3, C4, Cz, P3, P4, Pz, and Oz), mastoid derivations (M1 and M2), as well as left and right

electrooculogram (EOG) were referenced to Fpz online, all placed according to the international 10-20 system (Jasper 1958). In addition, a submental electromyogram (EMG) channel was recorded as a bipolar derivation.

EEG and EOG were re-referenced offline to average mastoid derivations (M1 and M2) and filtered from 0.3-35 Hz for EEG, 0.3-10 Hz for EOG and 10-50 Hz for EMG. Manual sleep stage scoring was completed using RemLogic analysis software (Natus, San Carlos, CA, USA) by a single expert scorer according to standard criteria (Iber et al., 2007; Rechtschaffen and Kales 1968). The sleep variables of interest obtained from the PSG recordings included total sleep time (TST; calculated as the total time spent asleep starting at sleep onset between "lights off" and "lights on"), the time in minutes spent in Stage 1 (NREM1) sleep, Stage 2 (NREM2) sleep, Stage 3 (NREM3) sleep, and rapid eye movement (REM) sleep. The percent duration of each stage from TST was also calculated. Sleep architecture results for both the sleep and nap groups are reported in **Supplemental Table 1**.

2.6. MRI acquisition and analysis

2.6.1. fMRI recording parameters. Functional Magnetic Resonance Imaging (fMRI) data was collected on a Siemens Biograph mMR 3.0 Tesla whole body MRI scanner (Siemens, Erlangen, Germany) using a 12-channel head coil. Anatomical images were acquired using a standard 3D Multislice MPRAGE sequence (TR = 2300 ms, TE = 2.98 ms, TI = 900 ms, FA = 9º, 176 slices, FoV = 256 × 256 mm^2, matrix size = 256 × 256 × 176, voxel size = 1 mm^3). In addition, multislice T2-weighted fMRI images were acquired during the resting-state acquisition (TR = 2.16 sec; TE = 30 ms, FA = 90º, 40 transverse slices, 3 mm slice thickness, 10% inter-slice gap, FoV = 220 x 220 mm^2, matrix size = 64 x 64 x 40, voxel size = 3.44 mm x 3.44 mm x 3 mm).

***2.6.2. Preprocessing*.** Resting-state images were preprocessed using the Matlab-based CONN toolbox v20.b (Whitfield-Gabrieli & Nieto-Castanon, 2012). Preprocessing was performed using the standard pipeline in CONN, comprising functional realignment, ascending order slice-timing correction, coregistration to the MPRAGE structural scan, spatial normalization, and spatial smoothing using an 8-mm full-width half-maximum (FWHM) isotropic Gaussian kernel filter. Segmentation was performed on the individual T1 images. Normalization to Montreal Neurological Institute (MNI) space was performed. The denoising pipeline was also employed, regressing out, from the realigned data, five noise components (for white matter and cerebral spinal fluid), and twelve motion effects (for *x*, *y*, and *z* translations, and for pitch, yaw, and roll rotations, and their first order derivatives). The data was then band-pass filtered from 0.008 – 0.09 Hz. Functional outliers were thresholded to the 97th Percentile. Scrubbing was performed using artifact detection tools with the threshold for global-signal exceeding 5 (z-value), and for subject-motion above 0.9 mm overall. Visual inspection ensured each participant did not show abnormalities. Averaged time-series for each ROI from the preprocessed images were extracted using CONN.

2.6.3. Seed regions. ROIs were computed as 6mm spheres around each coordinate using FSLeyes v0.34.2 (Wellcome Centre for Integrative Neuroimaging , London, UK, https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FSLeyes), and were subsequently exported to CONN. ROIs were defined *a priori*, obtained from the extant literature. Specifically, they were selected based on areas associated with sleep-related consolidation of procedural memory, including memory for cognitively complex skills and problem solving (*e*.g., caudate, OFC, dlPFC), and for regions typically implicated in a related motor sequence learning task (*e*.g., hippocampus, putamen, motor cortex. Coordinates for each region were determined from a companion study's task-

related peak activations (van den Berg et al., 2021). This yielded five anatomical seed regions (*i.e.*, hippocampus, caudate, motor cortex, OFC, and the dlPFC). In addition, the putamen is critically important for sleep-related procedural motor sequence learning (Albouy et al., 2015; Albouy et al., 2013c; Fang et al., 2021; Fogel et al., 2017; Vahdat et al., 2017a), and was thus, also included as an ROI (Vahdat et al., 2017). In total, six anatomical seed regions were included (**Table 1**; **Figure 2**). Coordinates for these ROIs had either unilateral activation exclusively in the right hemisphere, or in the case of regions with bilateral task-related activations, the right hemisphere demonstrated stronger peak activation.

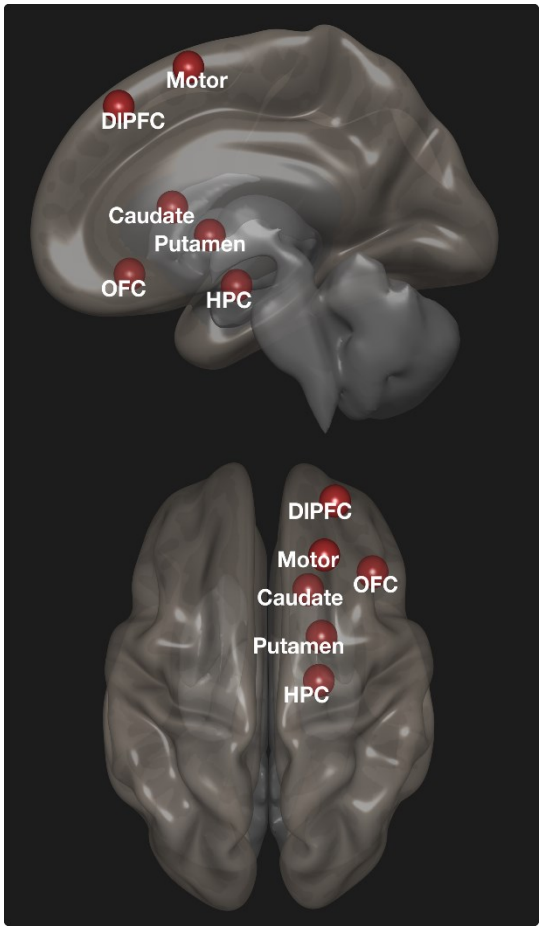

Table 1. *A priori* ROIs, using 6mm spheres drawn around task-related activation differences.

ROI	**Coordinates**		
	X	**Y**	**Z**
Caudate	20	16	10
Dorsolateral Prefrontal Cortex	30	36	46
Hippocampus	24	-8	-18
Inferior Orbitofrontal Cortex	44	32	-14
Motor	26	10	60
Putamen	25	2	0

Figure 2. *A priori* ROIs included in resting-state functional connectivity analyses.

2.6.4. ROI-to-ROI analyses. First, we examined changes in resting-state functional connectivity from before to after the training session (*i.e.,* Rest 2 > Rest 1) across all participants. In addition, we tested for group differences at *Rest 2* (*i.e.,* immediately following training) using a one-way ANOVA, to determine if groups differed in terms of their functional connectivity before the consolidation interval. No significant differences were observed from Rest 1 to Rest 2. These results are presented in the **Supplemental Text 1**.

To test our main hypotheses, we examined whether functional connectivity among our 6 ROIs changed from the resting-state scan immediately following the training session (*Rest 2*) to the resting-state scan immediately prior to the retest session (*Rest 3*) across an interval of sleep, nap, or wake. This was accomplished using a 3 x 2 Group (*Sleep, Nap, Wake*) by Session (*Rest 2, Rest 3*) ANOVA. Planned post-hoc comparisons were conducted between each group at *Rest 2* and *Rest 3*. All ROI-to-ROI *F*-tests and follow-up *t*-tests were thresholded at $p < 0.001$ uncorrected, with cluster-level correction for False Discovery Rate at $p_{FDR} < 0.05$ to control for multiple comparisons.

2.7 Brain-Behaviour Relationships. To further investigate if there were any brain-behaviour relationships from the ROI-to-ROI analyses described above, we entered performance improvements (speed and accuracy) as covariates of interest into the model to follow-up significant ROI-to-ROI effects. We report the result from the group by session interaction effect with ToH performance improvements as covariates of interest. This allowed us to assess the relationship between behavioural performance and changes in functional connectivity, from before to after the consolidation intervals in the Sleep *vs*. Wake, Nap *vs*. Wake, and Sleep *vs*. Nap comparisons.

2.8. Seed-to-Whole-Brain Analysis. To confirm the results of the hypothesis-driven, parsimonious *a priori* ROI-to-ROI approach, we employed a less constrained seed-to-whole-brain analysis using the six ROIs as seed regions. A 3 x 2 Group (*Sleep, Nap, Wake*) by Session (*Rest 2, Rest 3*) ANOVA was performed for each seed region. Planned comparison follow-up Group by Session ANOVAs tested for differences between: 1) Sleep *vs.* Wake, 2) Nap *vs.* Wake, and, 3) Sleep *vs.* Nap groups. All tests were performed using statistical thresholds of uncorrected $p < 0.001$ at the whole-brain level, and corrected for False-Discovery Rate $p_{FDR} < 0.05$ at the cluster level.

3. Results

3.1. Behavioural Performance. Briefly, performance improved over the course of the Training session; a block by trial ANOVA revealed a significant improvement in speed ($F(7,413) = 61.52$, $p < 0.0001$, $\eta^2 = 0.51$), accuracy ($F(7,413) = 12.65$, $p < 0.0001$, $\eta^2 = 0.17$), and speed-accuracy trade-off (SATO; $F(7,413) = 123.33$, $p < 0.0001$, $\eta^2 = 0.68$). Detailed supplemental results are discussed in a related paper (van den Berg et al., 2021).

Next, following the interval of sleep, nap, or wake, a one-way ANOVA showed significant differences between groups on percent task improvement for speed ($F(2,57) = 51.35$, $p < 0.0001$, $\eta^2 = 0.64$) and accuracy ($F(2,57) = 3.48$, $p = 0.038$, $\eta^2 = 0.11$), but not for SATO ($F(2,57) = 0.79$, $p = 0.459$, $\eta^2 = 0.03$). Follow-up *t*-tests indicated that the Sleep group outperformed the Wake group on speed ($t(38) = 6.69$, $p < 0.0001$, $d = 2.12$) and accuracy ($t(38) = 2.08$, $p = 0.044$, $d = 0.66$). The Nap group also outperformed the Wake group on speed ($t(38) = 8.86$, $p < 0.0001$, $d = 2.80$) and accuracy ($t(38) = 2.36$, $p = 0.024$, $d = 0.75$). Finally, and surprisingly, the Nap group improved more than the Sleep group on speed ($t(38) = 4.11$, $p < 0.001$, $d = 1.30$). Thus, either a full night of sleep or a daytime nap benefitted task performance in terms of speed and accuracy more so than a period of wakefulness (**Figure 3**).

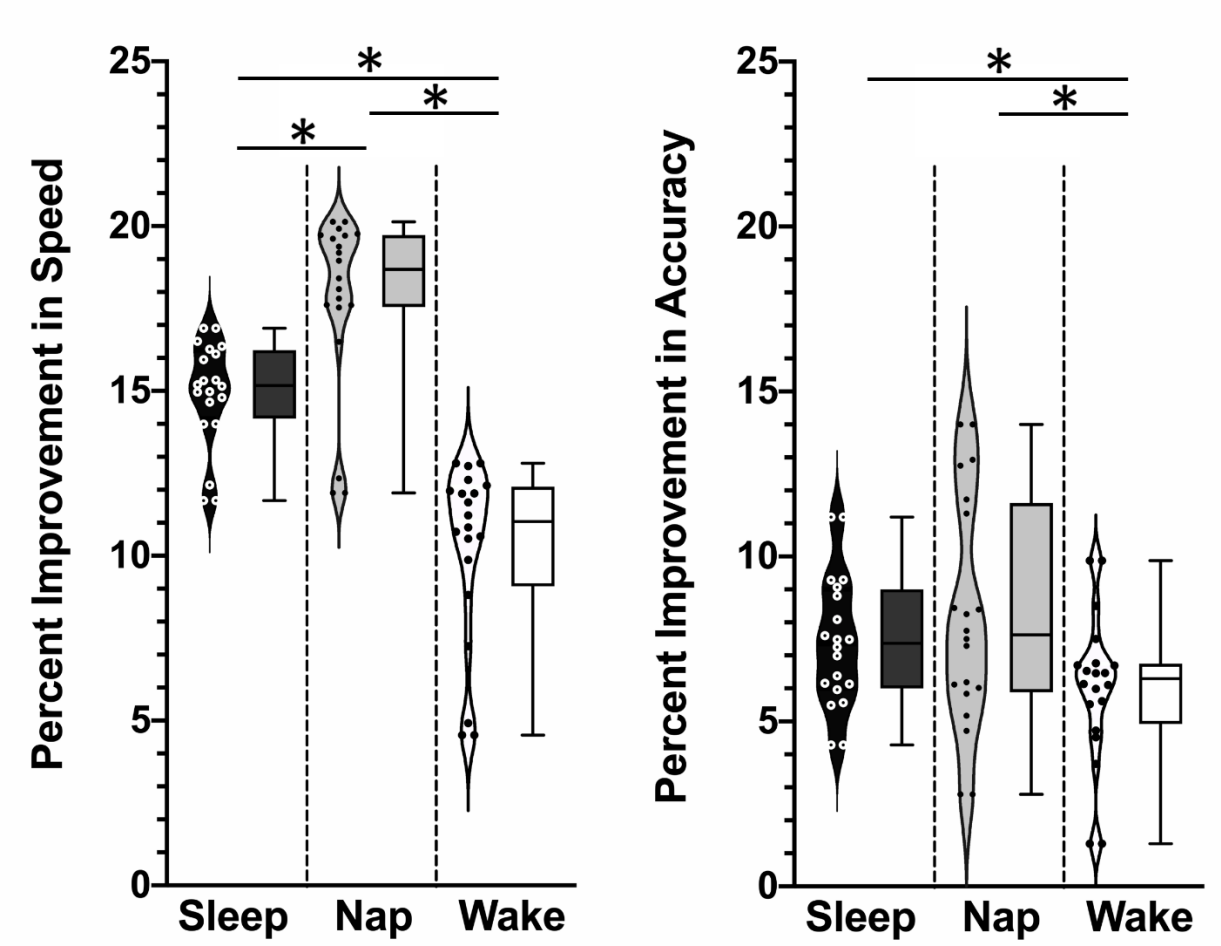

Figure 3. Behavioural Results. Offline gains in ToH performance (expressed as percent improvement in speed and accuracy) from Training to Retest for Sleep, Nap and Wake groups.

3.2. Resting-state functional connectivity results

3.2.1. ROI-to-ROI results. To test our main research question employing a hypothesis-driven *a priori* set of 6 ROIs, a single 3 x 2 Group (*Sleep, Nap, Wake*) by Session (*Rest 2, Rest 3*) ANOVA, to analyze all 6 ROIs using the same model while correcting for multiple (pairwise) comparisons, revealed differences in functional connectivity from Rest 2 to Rest 3 as a function of group ($F(4,112) = 3.17$, $p_{FDR} = 0.049$). To further investigate the between-group differences from Rest 2 to Rest 3, follow-up 2 (Group) x 2 (Session) ANOVAs revealed that this connectivity difference was specific to the Sleep *vs.* Wake comparison ($F(1,38) = 8.11$, $p_{FDR} = 0.042$), and not the Nap *vs*. Wake (all $p_{FDR} > 0.550$), or Sleep *vs*. Nap (all $p_{FDR} > 0.590$)

comparisons. Independent *t*-tests revealed that connectivity increased between the hippocampus and the inferior OFC from Rest 2 to Rest 3 in the Sleep *vs*. Wake group ($t(38) = 2.85$, $p_{FDR} = 0.035$; **Figure 4**). Individual hippocampal-orbitofrontal connectivity values at Rest 2 and at Rest 3 separately, for each participant in each group, are descriptively shown in **Figure 5**.

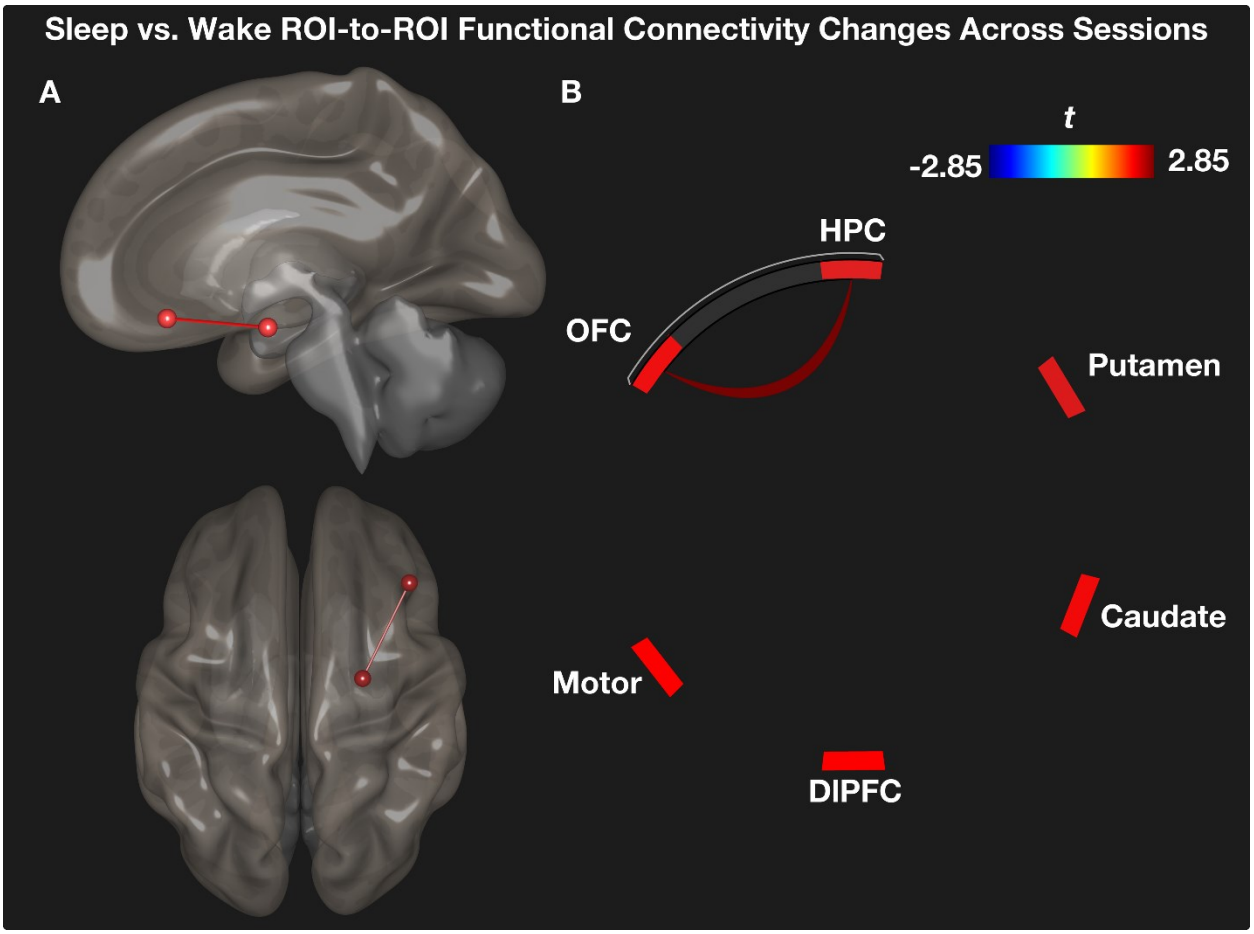

Figure 4. ROI-to-ROI results using 6 *a priori* ROIs. The hippocampus showed strengthened functional connectivity to the inferior OFC following a period of Sleep *vs.* Wake. Significant edge between ROIs reflects independent *t*-test value. Abbreviations: Hippocampus (HPC); Dorsolateral Prefrontal Cortex (DlPFC); Orbitofrontal cortex (OFC).

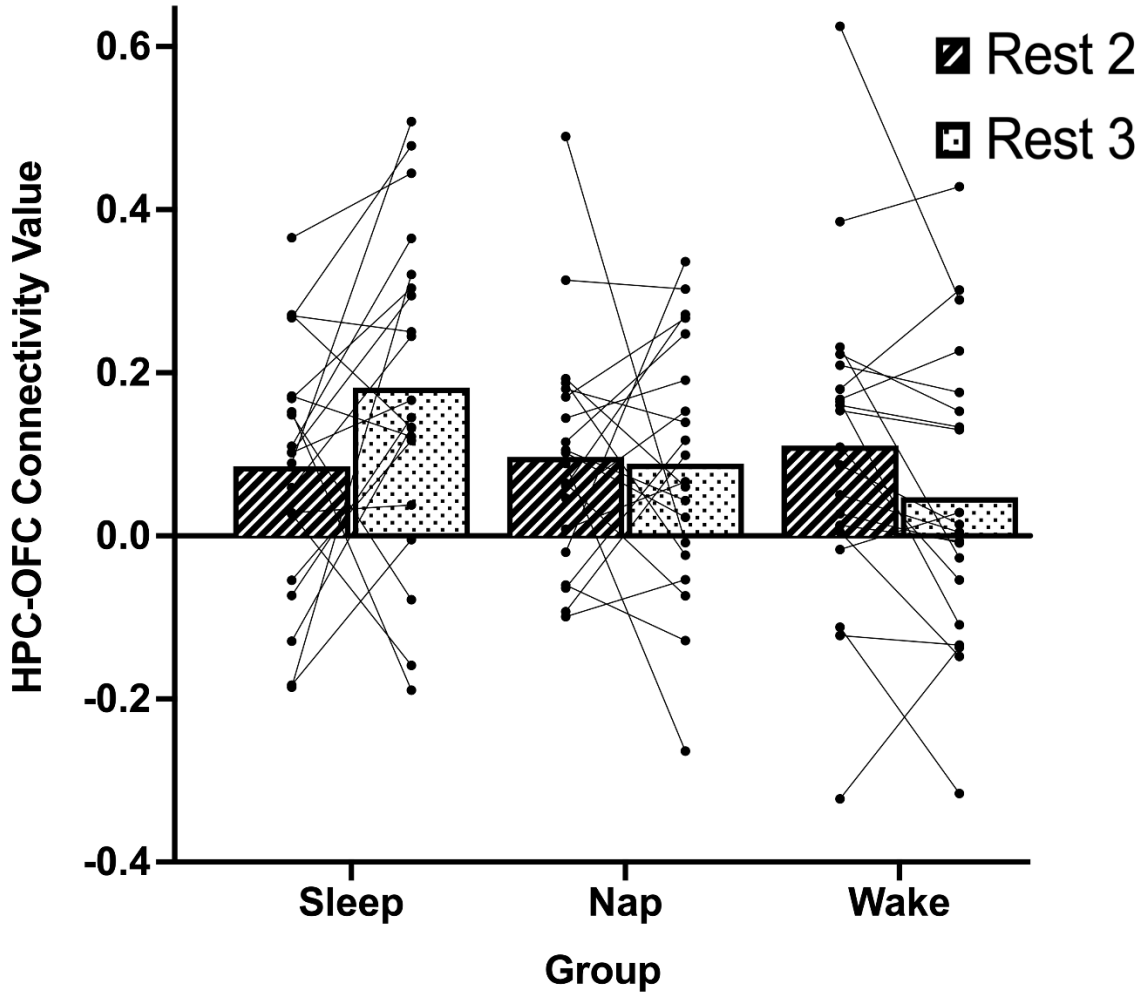

Figure 5. Individual and group mean hippocampal-orbitofrontal resting-state functional connectivity values at both Rest 2 and Rest 3, for Sleep, Nap, and Wake groups. The Sleep group showed increased functional connectivity, the Nap group showed stabilization, and the Wake group showed decreased functional connectivity.

3.2.2. Seed-to-whole-brain results. In order to confirm the ROI-to-ROI results in a less-constrained and more exploratory analysis approach, a series of 3 x 2 Group (*Sleep, Nap, Wake*) by Session (*Rest 2, Rest 3*) ANOVAs using the 6 ROIs as seeds revealed significant changes in connectivity as a function of group between the hippocampus and bilateral supplementary motor area (SMA; $F(2,57) = 12.59$, $p_{FDR} = 0.046$, $k = 92$; **Figure 6A**), and between the putamen and the left anterior cerebellum ($F(2,57) = 18.39$, $p_{FDR} = 0.040$, $k = 95$; **Figure 6B**). Planned comparison follow-up 2 x 2 Group by Session ANOVAs showed that these omnibus effects, in

both cases, were specific to the Sleep *vs.* Nap comparison, whereby functional connectivity among these areas was greater in the Sleep group (**Table 2**).

These planned follow-up comparisons yielded additional differences in seed-to-whole-brain functional connectivity between two groups, which were not observed in the omnibus test between all three groups. Specifically, the Sleep *vs.* Nap comparison additionally demonstrated increased functional connectivity between the OFC and SMA, the dlPFC and the temporal pole, and decreased connectivity between the putamen and precentral/paracentral cortices. In addition, similar to the ROI-to-ROI analysis, the Sleep group (when compared to the Wake group) showed increased connectivity between the hippocampus and the OFC, between the lateral and medial OFC, and also, between the caudate and somatosensory area. By comparison, the Nap group (when compared to the Wake group) showed negative functional connectivity from the motor cortex to the cuneus and to the supramarginal gyrus.

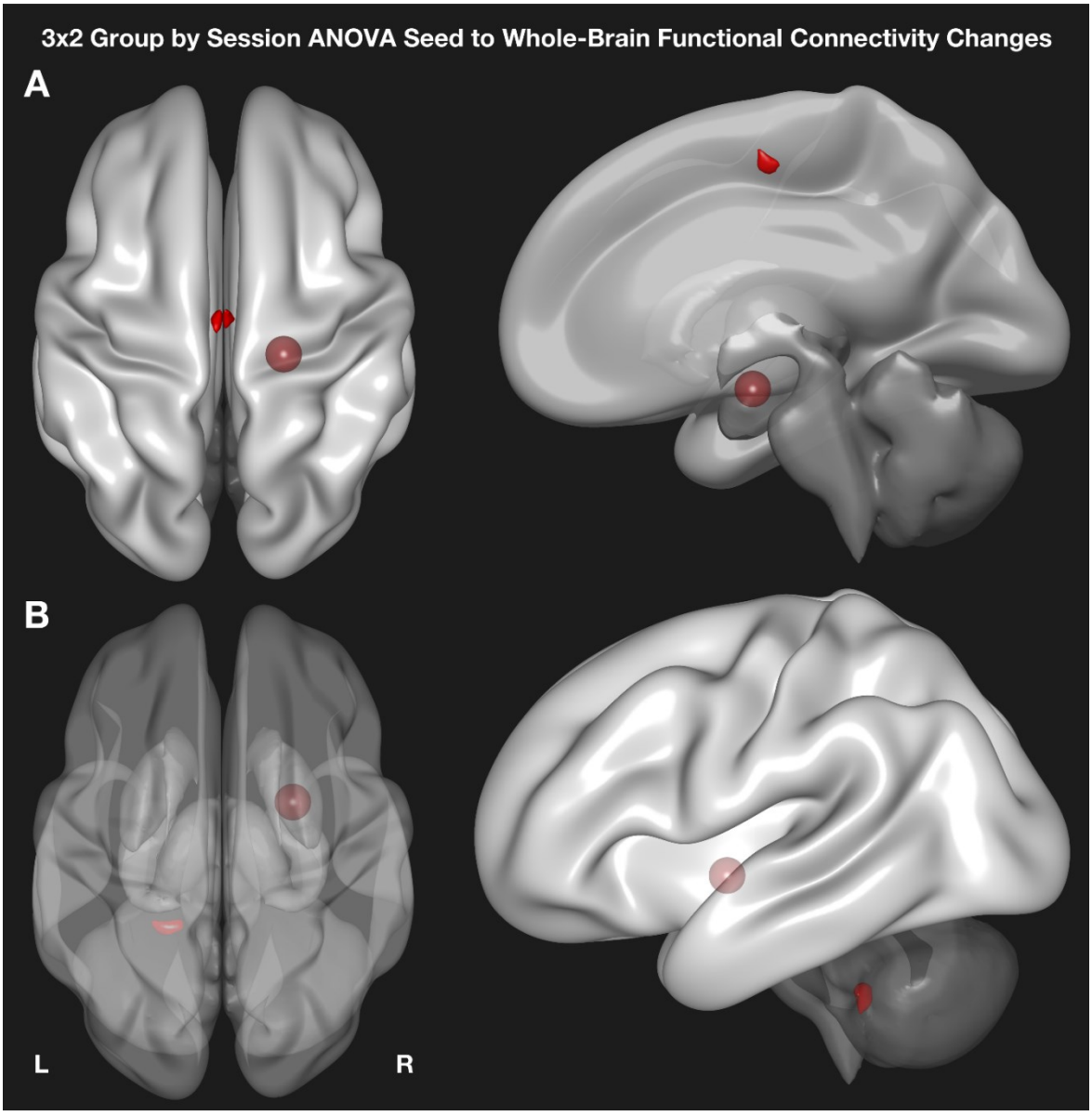

Figure 6. Seed-to-whole-brain analyses using a 3 x 2 Group (*Sleep, Nap, Wake*) by Session (*Rest 2, Rest 3)* ANOVA demonstrated changes in functional connectivity between (**A**) the hippocampus and SMA; and between (**B)** the putamen and anterior cerebellum**.** Both omnibus effects were specific to the Sleep *vs.* Nap comparison, as suggested by follow-up 2x2 Group by Session ANOVAs (**Table 2**). Spheres represent seeds.

Table 2. Seed-to-Whole-Brain analyses between groups at post-interval (Rest 3; R3) minus pre-interval (Rest 2; R2). Significant results thresholded to cluster size $p_{FDR} = 0.05$. *K* = # of voxels (size of cluster).

Sleep *vs.* Wake (Rest 3 – Rest 2)

		Target Coordinates							Direction R2 to R3	
L/R	**Seed**				**Target**	***K***	***t*(38)**	**p-FDR**	**Sleep**	**Wake**
R	Caudate	36	-32	72	Somatosensory	349	5.18	<0.001	↑	↓
R	HPC	8	50	-16	OFC	184	4.75	0.008	↑	↓
R	Inf. OFC	-6	-78	-14	Lingual Gyrus	130	3.32	0.039	↑	↓
		-10	56	-4	OFC	131	-5.15	0.029	↓	↑
R	dlPFC		--		--	--	--	--	--	--
R	Motor		--		--	--	--	--	--	--
R	Putamen		--		--	--	--	--	--	--

Nap *vs.* Wake (Rest 3 – Rest 2)

		Target Coordinates							Direction R2 to R3	
L/R	**Seed**				**Target**	***K***	***t*(38)**	**p-FDR**	**Nap**	**Wake**
R	Caudate		--		--	--	--	--	--	--
R	HPC		--		--	--	--	--	--	--
R	Inf. OFC		--		--	--	--	--	--	--
R	dlPFC		--		--	--	--	--	--	--
R	Motor	22	-74	20	Calcarine fissure	430	-6.08	<0.001	↓	↑
		50	-32	38	Supramarg. Gyrus	253	-5.24	<0.001	↓	↑
R	Putamen		--		--	--	--	--	--	--

Sleep *vs.* Nap (Rest 3 – Rest 2)

		Target Coordinates							Direction R2 to R3	
L/R	**Seed**				**Target**	***K***	***t*(38)**	**p-FDR**	**Sleep**	**Nap**
R	Caudate		--		--	--	--	--	--	--
R	HPC	0	-16	52	SMA	153	4.65	0.021	↑	↓
		14	-20	52	SMA	120	5.71	0.031	↑	↓
R	dlPFC	-54	14	-4	Temporal Pole	346	6.28	<0.001	↑	↓
R	Inf. OFC	4	-6	52	SMA	143	5.59	0.034	↑	↓
R	Motor		--		--	--	--	--	--	--
R	Putamen	-24	-44	-42	Ant. Cerebellum	161	5.72	0.006	↑	↓
		46	-8	42	Precentral	115	-4.7	0.042	↓	↑
		-4	-12	72	Paracentral lobule	93	-4.91	0.042	↓	↑

3.3. Brain-behaviour relationships. We entered behavioural gains as covariates of interest into the model to follow-up the ROI-to-ROI analysis, to examine the relationship between functional connectivity changes and behavioural improvements. A 2 x 2 Group (*Sleep, Wake*) by 2 Session (*Rest 2, Rest 3*) ANCOVA, entering accuracy as a covariate of interest, assessed the contribution of the group by accuracy interaction term (between-subjects independent variable) and the resting-state session (within-subjects independent variable) on the strength of functional connectivity (dependent variable) among the 6 ROIs. This analysis revealed that the relationship between the improvement in accuracy and the extent of the change in functional connectivity (Rest 2 to Rest 3) differed between the Sleep *vs*. Wake groups for the hippocampal-orbitofrontal cortex edge ($F(2,55) = 5.08$, $p_{FDR} = 0.028$; **Figure 7**). Similar ANCOVAs comparing Sleep *vs.* Nap, and Nap *vs.* Wake, showed no significant effects. Significant correlations were not observed for any comparison when entering improvement on speed as a covariate of interest. Thus, the change in HPC-OFC functional connectivity from Rest 2 to Rest 3 was associated with the differential relationship in behavioural accuracy gains scores between Sleep *vs*. Wake comparisons, whereby the correlation was more positive in the Sleep *vs*. the Wake group.

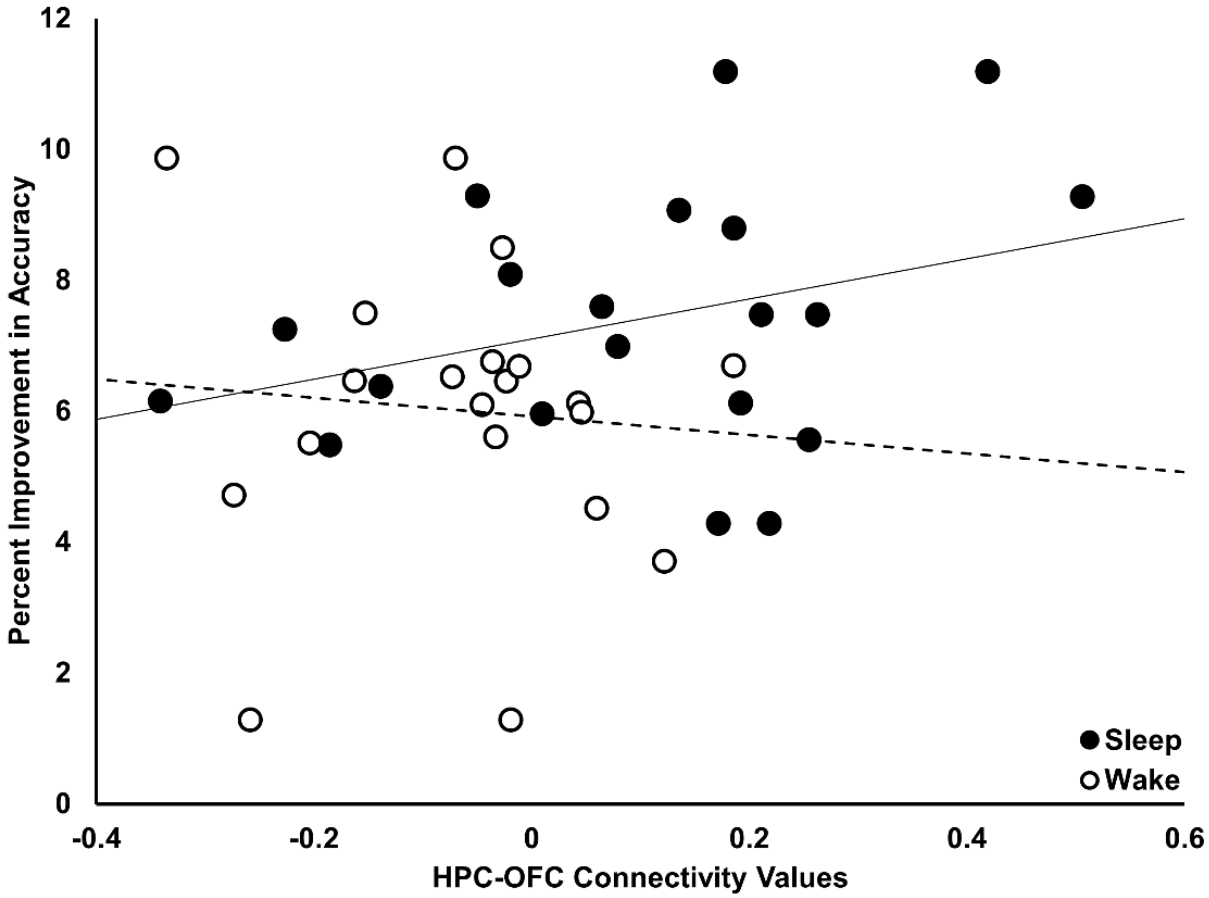

Figure 7. Interaction between Sleep and Wake groups on the relationship between percent improvement in accuracy on the Tower of Hanoi and the change in hippocampal-orbitofrontal cortex functional connectivity from Rest 2 to Rest 3. Abbreviations: Hippocampus (HPC); Orbitofrontal cortex (OFC).

4. Discussion

Previous studies have revealed that the hippocampal-striatal-cortical network of brain areas is involved in the consolidation of procedural memory for motor skills (Albouy et al., 2013c, 2013b). This consolidation process preferentially benefits from a period of sleep (Debas et al., 2010; Boutin et al., 2018; Fang et al., 2021). In the present study, we observed: **1)** improved performance on the ToH when sleep (either nocturnal sleep, or a daytime nap) occurred during the consolidation interval as compared to a period of wake; **2)** strengthened functional connectivity from Rest 2 to Rest 3 in key brain areas associated with the acquisition of novel cognitive strategies and procedural problem-solving skills; **3)** these changes in functional

connectivity differed following a consolidation period of sleep as compared to either a daytime nap, or a period of wakefulness, and; **4)** the extent of the strengthened functional connectivity between hippocampal-orbitofrontal areas was more positively correlated with the offline behavioural improvements in problem-solving skills in the Sleep group than in the Wake group.

4.1. The role of subcortical–cortical communication in problem-solving skills. It has been said that "*neurons wire together if they fire together*" (Hebb, 1949). At the systems level, for most types of memory, this process initially involves a dialogue between the hippocampus and neocortical areas. Sleep is thought to be an opportune time for this transformation of the memory trace to take place, which is apparent through sleep-dependent interactions between hippocampal-putamen areas (Debas et al., 2010; Barakat et al., 2013; Albouy et al., 2015), hippocampal-caudate areas (Cousins et al., 2016; van den Berg et al., 2021), striatal-cortical areas (Debas et al., 2014; Vahdat et al., 2017; Fang et al., 2021), and hippocampal-prefrontal areas (Samanta et al., 2021). During the offline consolidation period of sleep, cortical functional connectivity is decreased, whereas subcortical functional connectivity is increased (Vahdat et al., 2017). Notably, the putamen is a central hub of connectivity, and the strength of the within-network connectivity of the putamen is associated with offline improvements in motor sequence learning (Vahdat et al., 2017). Following the offline consolidation period (*i.e.,* upon awakening), subcortical-cortical resting-state functional connectivity is, remarkably, reinstated (Vahdat et al., 2017). In addition, functional communication between the putamen and motor cortex is increased following a consolidation interval of daytime sleep, as compared to an equivalent period of wake (Fang et al., 2021). In summary, a post-learning period of sleep transforms the memory trace via an interaction between the hippocampus, striatum and prefrontal cortex.

The results of the present study complement these recent findings and extend knowledge of how sleep is correlated with sleep-related offline gains in performance for novel cognitive strategies needed to solve problems. Interestingly, unlike motor skills memory consolidation, the strengthening of subcortical-cortical communication following a period of nocturnal sleep *vs*. daytime wakefulness appears to involve the hippocampus and OFC, but not the putamen. This was observed in both a hypothesis-driven ROI-to-ROI analysis, and in a complementary, but less constrained seed-to-whole-brain approach, which contains more stringent thresholds for statistical significance. Follow-up analyses revealed that the extent of the change in functional connectivity over the consolidation interval was differentially correlated with performance improvements, depending on whether this interval contained either nocturnal sleep or daytime wakefulness. These results suggest that sleep-related changes in hippocampal-OFC functional connectivity are associated with offline gains in problem-solving skills.

4.2. The role of the striatum in problem-solving skills. The involvement of the striatum evolves as consolidation of simple motor procedural skills progresses over time (Lehéricy et al., 2005). Changes in functional connectivity in the striatum have been shown during (Vahdat et al., 2017) and following (Fang et al., 2021) a consolidation period of sleep. Communication between the putamen and other task-relevant brain areas is critical for simple motor sequence memory consolidation. Interestingly, unlike previous studies focused on the consolidation of simple motor skills, we observed enhanced connectivity with the caudate nucleus (to the somatosensory cortex), instead of the putamen in the Sleep *vs.* Wake comparison. Moreover, the putamen showed changes in functional connectivity only in the Sleep *vs.* Nap comparison. Thus, a full night of sleep might be involved in enhancing communication in regions involved in planning

and problem solving (*e.g.,* caudate), whereas a daytime nap might be involved in enhancing communication in brain areas involved in motor skills and motor execution (*e.g*., putamen).

4.3. The role of the hippocampus in problem-solving skills. Strengthened functional connectivity between the hippocampus and the OFC, and improved problem-solving skills, were both observed following a full night of sleep (when compared to a day of wakefulness). This hippocampal-OFC strengthening across sessions was specific to nocturnal sleep relative to daytime wake, as demonstrated by both ROI-to-ROI, and also, the less-constrained, and more exploratory seed-to-whole-brain analyses. Importantly, the magnitude of this strengthened hippocampal-OFC functional connectivity was more positively correlated with performance improvements in the Sleep group when compared to the Wake group). Prior research shows the hippocampus and OFC work together during trial-and-error performance (Hornak et al., 2002) or goal-directed strategy switching (Young & Shapiro 2011). Consistent with these previous studies, our results suggest that hippocampal-OFC communication is associated with sleep-related offline gains in procedural skills involving the acquisition of novel cognitive strategies. This further suggests that enhanced functional communication at the systems level is associated with improved performance at the behavioural level, which occurs preferentially during sleep compared to wake.

4.4. Differential effect on functional connectivity between sleep, nap, and wake. Previous studies have shown that for certain types of procedural memory consolidation, for example perceptual memory (Mednick et al., 2003), or memory for motor sequences (Doyon et al., 2009), a nap is just as beneficial as a night of sleep. However, at the neuronal systems-level, for changes that take place in brain areas which support higher-order problem-solving skills, an additional benefit comes from a longer period of sleep compared to either a day of wake or a

daytime nap (van den Berg et al., 2021). Here, we show that a full night of sleep but not a daytime nap strengthens striatal- and hippocampal-neocortical communication in areas involved in memory for cognitive strategies and problem-solving skills.

Specifically, seed-to-whole-brain analyses (**Table 2**) revealed that the Sleep group showed relatively strengthened functional connectivity between the caudate and somatosensory areas, and between the hippocampus and the OFC, as compared to the Wake group. Meanwhile, the Sleep *vs.* Nap comparison showed increased functional connectivity for the Nap group in areas associated with simple motor skills, for example between the putamen and cerebellum. These findings suggest that the changes following a nap involve brain areas which support the execution of the task, but not the cognitive strategy *per se*. By contrast, sleep-related increased functional communication was observed for hippocampal and OFC seeds with areas involved in mental imagery for motor movements (*i.e.,* the SMA; Mizuguchi, Suezawa, & Kanosue, 2019). No significant ROI-to-ROI differences were observed when comparing Nap *vs.* Wake groups for the hippocampus or OFC as seed regions; however, the less constrained seed-to-whole brain approach revealed that the Nap *vs*. Wake comparison showed increased negative functional connectivity between the motor cortex and the cuneus, and between the motor cortex and supramarginal gyrus. Thus, we speculate that while behavioural performance improvements can benefit from even a short period of daytime sleep (involving primarily motor cortical and related areas), a full night of sleep is optimal for more complete systems-level consolidation (involving hippocampal and related areas).

Importantly, this does not lead to the conclusion that fewer or less important changes in functional communication occur from a daytime nap (as compared to wake), only that any changes in functional communication between brain areas during the resting state are not as

robust or complete after only a nap. Moreover, we have previously shown that measures other than resting-state functional connectivity (*e.g.*, enhanced brain activation) unfold following a nap. Indeed, in a related paper (van den Berg et al., 2021), we show that a nap strengthens activation of the parietal, motor, and prefrontal cortices, along with reduced activation of the hippocampus – but, sleep does afford an additional boost to this memory trace strengthening, over-and-above a nap, or a period of wake.

The differential pattern of behavioural improvements and functional connectivity in the Nap group might also indicate that consolidation is sensitive to time-of-day effects. At the neural systems level, functional networks become less independent of one another following sleep deprivation (Chee & Zhou, 2019) or when vigilance is impaired (Thompson et al., 2013). In other words, functional networks are generally more segregated when the brain is well-rested. In the present study, it is possible that testing at different times of day between Sleep and Nap groups, and in turn, differences in these network segregations, might explain the differences observed between groups. However, it is unlikely that this confounds our results for two reasons. First, rather than identifying greater segregation between brain areas following sleep (*i.e., decreases* in functional connectivity), our findings are in the opposite direction and show *increased* functional connectivity between ROIs in Sleep *vs.* Wake, with minimal changes in the Nap *vs.* Wake comparisons (**Table 2**). Second, the brain-behaviour analyses showed that the changes in functional connectivity were correlated with the extent of performance improvements. This correlation was more positive in the Sleep group than in the Wake group; Naps did not show a significant correlation with behavioural improvement, thus, this pattern of correlations cannot be easily explained by time-of-day alone.

Nonetheless, it is important to note that that the time interval between Rest 2 and Rest 3 was shorter in the Nap group (*i.e.,* ~5 hours), than in the ~10-hour intervals in the Sleep and Wake groups. The improved task performance in the Nap group might be attributable to the effects of a short daytime sleep period, or alternatively, to a shorter time window between test and retest. A separate, 90-minute, daytime wake group could clarify whether the behavioural effects are due specifically to a nap, or to the time interval.

Another alternative interpretation for the greater behavioural improvements following a nap, is that sleep affords protection from interference, rather than enhanced performance (Rickard et al., 2008). Offline periods of quiet rest have shown evidence for 'wake-dependent stabilization' (Craig et al., 2018; Humiston & Wamsley, 2018). This however, does not appear to be a plausible explanation, given that previous work on this same memory task (*i.e.,* ToH), showed that improvement in performance is observed after sleep, and only after sleep (*e.g.,* van den Berg et al., 2019). This alternative explanation is also not easily explained by the Wake group in the current study, as a period of quiet wake has been shown to afford a similar protective effect as a sleep period (Craig et al., 2018; Humiston & Wamsley, 2018). Thus, the improved behavioural performance in our study following a nap cannot be explained by wake-dependent stabilization, or the simple passage of time.

Finally, it is possible that dissimilar effects of sleep and nap on functional connectivity may depend on nap architecture. In particular, REM sleep that occurs during a nap is shown to protect perceptual memories from interference (McDevitt et al., 2015). In addition, the presence of REM during a daytime nap can enhance perceptual memory consolidation to the same degree as a night of sleep. Specifically, it has been shown that naps that contained REM sleep enhanced subsequent performance, as compared to either naps without REM sleep, or an equivalent period

of wakefulness (Mednick et al., 2003). In the current study, 75% (n=15) of participants in the Nap group reached a single period of REM sleep, which may be insufficient to achieve the same extent of consolidation as a night of sleep. However, supplemental correlation analyses (**Supplemental Table 2**) did not reveal any significant relationships between REM sleep duration and either ToH performance improvements or hippocampal-orbitofrontal connectivity values in either the Nap or Sleep groups.

4.5. Limitations and future directions. We selected a parsimonious number of ROIs in a hypothesis-driven approach, to assess how functional connectivity changes within the hippocampal-striatal-cortical network of brain areas following a consolidation period of sleep, nap, or wake. These ROIs were selected based on peak coordinates in task-related activations areas of interest most consistently associated with sleep-related consolidation of procedural memories that comprise both strategy learning and problem-solving skills. However, the trade-off of this focused approach comes at the expense of limited exploration of whole-brain connectivity. We mitigated this limitation by including a complementary seed-to-whole-brain analysis, thus permitting us to examine how our ROIs functionally communicate with the rest of the brain.

In addition, it is worth noting that our ROIs were coincidentally all in the right hemisphere. ROIs were determined by task-related activations which demonstrated either unilateral activation exclusively in the right hemisphere, or in the case of regions with bilateral task-related activation, the right hemisphere consistently had stronger peak activations (van den Berg et al., 2021). Furthermore, these activations were ipsilateral to performance with right-handed task performance, which is consistent with meta-analysis findings of primarily right (ipsilateral) response activations in subcortical areas, which support spatial behaviours (Cieslik et

al., 2015). A possible explanation of this finding is that, for memory consolidation of cognitive strategies rather than motor skills, there is less emphasis on the kinesthetic motor sequence itself, and more emphasis on either the cognitive strategy or spatial component. In this way, the brain hemisphere contralateral to the limb movement executing the task is less involved in the memory consolidation process. However, this is speculative and is an avenue for further research.

As discussed above (see section ***4.4. Differential effect on functional connectivity between sleep, nap, and wake***), time-of-day is an important consideration when comparing resting-state functional connectivity between intervals containing sleep or wake. Future neuroimaging studies could directly investigate this, by including fMRI acquisitions using an AM-PM-AM *vs.* PM-AM-PM group testing paradigm (van den Berg et al., 2019). Our group has previously used this paradigm in a behaviour-only study for the ToH. This study revealed that improvement on the ToH occurs once given the opportunity to sleep (*i.e.*, PM-to-AM), regardless of whether initial learning occurs in the AM or PM. Inclusion of pre-post resting-state acquisitions at each time point, as well as the inclusion of a daytime nap group would allow for changes in brain activation and resting-state functional connectivity while examining time-of-day effects to be explored.

In addition, it is important to note that the observed changes in functional connectivity, and their relationship to memory consolidation is entirely correlational. Including a condition using the same fMRI protocol, but where a control task is used, would allow for stronger evidence that changes in functional connectivity are indicative of memory consolidation *per se*, rather than a generalized benefit of sleep. Alternatively, simultaneous EEG-fMRI acquisitions during sleep would enable the investigation of memory trace reactivation in different sleep stages, and time-locked to micro-architecture of sleep (*e.g.*, spindles, slow waves, eye

movements), which would provide additional insight into how sleep actively participates in the memory consolidation process as it happens, rather than observing changes before and after sleep. Similarly, nocturnal sleep studies with more extensive investigation of the features of sleep that might changes in response to this type of new learning, would reveal the electrophysiological markers of sleep-related memory consolidation.

Finally, future studies could employ a similar approach to investigate the relationship between sleep and other forms of memory (*e.g.*, motor sequence learning, declarative memory). Specifically, ROI coordinates obtained from memory domain-specific neural activity can be examined during resting-state periods across the consolidation interval. This would also help to elucidate the specificity of the results of the current study.

5. Conclusion

These findings are consistent with recent evidence that the hippocampus is involved in sleep-related procedural memory consolidation not only for simple procedural motor sequences (Albouy et al., 2013a; Albouy et al., 2013b; Fogel et al., 2017; Boutin et al., 2018) but also for motor sequences that involve the acquisition of novel cognitive strategies required to solve problems (Cousins et al., 2016; van den Berg et al., 2021). Overall, our results suggest that a full night of sleep (compared to wake) strengthens functional communication between the hippocampal-striatal-cortical network of brain areas, and that this enhanced functional communication is distinct from a daytime nap – even though behavioural improvements occur following sleep and nap. Finally, the changes in hippocampal-orbitofrontal functional connectivity following nocturnal sleep compared to daytime wake were associated with improved memory for cognitive strategies and problem-solving skills.

6. Acknowledgments

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Supplemental Material

Table S1. **Correlation between sleep architecture, behavioural improvement and hippocampal-orbitofrontal connectivity for the sleep and nap conditions**. Correlations for REM sleep in the nap condition based on those who reached REM sleep n=15. All other correlations based on n=20 for both conditions. * p < 0.05.

Sleep Group						
Sleep Architecture	**Accuracy**		**Speed**		**HPC-OFC Connectivity**	
	r	**p**	**r**	**p**	**r**	**p**
Sleep Efficiency (%)	-0.152	0.522	-0.003	0.991	0.15	0.529
NREM1 (mins)	0.115	0.630	-0.109	0.646	-0.387	0.092
NREM2 (mins)	-0.099	0.676	-0.159	0.502	0.139	0.559
NREM3 (mins)	-0.531	0.016*	-0.392	0.087	-0.224	0.343
REM (mins)	-0.019	0.935	0.182	0.441	0.206	0.384
TST (mins)	-0.331	0.153	-0.196	0.408	-0.028	0.906
WASO (mins)	0.124	0.602	-0.029	0.904	-0.245	0.297
Awakenings (#)	0.010	0.965	0.047	0.845	-0.263	0.263
Nap Group						
Sleep Architecture	**Accuracy**		**Speed**		**HPC-OFC Connectivity**	
	r	**p**	**r**	**p**	**r**	**p**
Sleep Efficiency (%)	-0.280	0.232	-0.348	0.133	0.105	0.660
NREM1 (mins)	-0.156	0.510	0.082	0.731	0.097	0.684
NREM2 (mins)	-0.313	0.180	-0.195	0.410	-0.293	0.210
NREM3 (mins)	0.195	0.409	0.060	0.802	0.262	0.265
REM (mins)	-0.320	0.245	-0.410	0.120	0.145	0.606
TST (mins)	-0.300	0.199	-0.309	0.184	0.065	0.785
WASO (mins)	0.271	0.249	0.345	0.136	-0.176	0.458
Awakenings (#)	-0.008	0.974	0.265	0.259	-0.412	0.071

Table S2. Experimental session sleep architecture for Sleep and Nap conditions. Percentages expressed in minutes as a proportion of total sleep time.

	Sleep Condition		Nap Condition	
Sleep Variable	**M**	**SD**	**M**	**SD**
NREM1 (mins)	17.23	15.28	5.63	4.52
NREM2 (mins)	227.10	34.73	36.92	12.76
NREM3 (mins)	74.90	22.51	20.04	15.76
REM (mins)	86.06	23.86	6.21	5.52
WASO (mins)	42.01	30.12	13.21	12.85
NREM1 (%)	4.25	4.58	8.18	7.85
NREM2 (%)	56.03	5.88	53.67	16.36
NREM3 (%)	18.48	5.64	29.13	18.80
REM (%)	21.23	4.93	9.02	8.06
WASO (%)	10.36	7.43	19.2	18.6
TST (mins)	405.29	42.58	68.79	13.62
Sleep Efficiency (%)	87.59	7.70	77.97	14.56
Awakenings (#)	30.7	7.71	6.15	3.54

S1: ROI-to-ROI Analysis: Training Session

Resting-state functional connectivity from before to after the Tower of Hanoi training session *i.e.,* Rest 2 > Rest 1 did not significantly change for any connections among our 6 ROIs. This was demonstrated by examining change from Rest 1 to Rest 2 across all participants all $p_{FDR} \geq 0.49$, and between groups as examined through a 3x2 Group by Session ANOVA all $p_{FDR} \geq 0.27$. A one-way ANOVA at Rest 2 comparing Sleep, Nap, and Wake groups also showed no significant differences in functional connectivity all $p_{FDR} \geq 0.82$.

These results from the initial training period suggest that as expected, any observed changes in functional connectivity across the consolidation interval of sleep, nap, or wake could not be attributed to differences before the consolidation interval.

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Chapter 5: General Discussion & Conclusion

1. Summary of Findings

The purpose of this thesis was to identify the neurobiological and electrophysiological substrates of sleep-dependent memory consolidation for cognitive strategies and problem-solving skills. This work identifies the 1) electrophysiological correlates, 2) cerebral activation, and 3) functional communication underlying this consolidation process. More specifically, this series of studies show that eye movements during phasic and tonic REM sleep are biomarkers of neuronal oscillations (*i.e.,* theta rhythms and SMR) associated with memory consolidation, and that greater activity and communication between the hippocampus, caudate, prefrontal and motor cortices support sleep-dependent memory consolidation. These findings are in line with the Active Systems Consolidation Hypothesis, whereby sleep plays an active role in transforming the recently acquired memory trace into a strengthened and more easily retrievable form (Diekelmann & Born, 2010; Marshall & Born, 2007; McClelland et al., 1995).

Much attention has been given to the role of sleep in consolidating procedural memory for simple motor sequences. Not only is the hippocampal-striatal-cortical network of brain areas involved in this process (Albouy et al., 2008, 2012; Albouy, King, et al., 2013; Albouy, Vandewalle, et al., 2013; Debas et al., 2010; Fogel, Albouy, King, et al., 2014; Fogel et al., 2017; Vahdat et al., 2017), but the reactivation and subsequent strengthening of putamen activity is time-locked to NREM sleep spindles (Boutin et al., 2018; Fogel et al., 2017; Vahdat et al., 2017). By contrast, REM sleep does not appear to consolidate simple motor skills (Djonlagic et al., 2020; Laventure et al., 2016; Mednick et al., 2013). Rather, only when the procedural memory involves the acquisition of cognitive strategies and problem-solving skills is REM sleep involved (Brand et al., 2010; Fogel et al., 2015; Smith, Nixon, et al., 2004; Smith & Lapp, 1991; Smith & Weeden, 1990), and at the behavioural level, cognitive strategies and problem-solving skills show a

preferential benefit of sleep-related consolidation over-and-above the accompanying motor skills (van den Berg et al., 2019). These previous behavioural findings, alongside the existing knowledge on the neural correlates of sleep-related consolidation of procedural memory for simple motor sequences, lay the groundwork for this thesis, the aim of which was to understand how sleep consolidates procedural memory for cognitive strategies and problem-solving skills.

2. Performance Improvements in Procedural Memory for Cognitive Strategies and Problem-Solving Skills

2.1. Performance improvements. The ToH was employed to assess problem-solving skills that require the acquisition of a novel cognitive strategy. Performance improvements on the ToH were compared across three pre *vs*. post experimental conditions, comprising a consolidation interval of either: 1) a nocturnal sleep, 2) a daytime nap, or, 3) daytime wakefulness. It was hypothesized that the behavioural improvements would be greatest following a full night of sleep and weakest following a day of wakefulness, with a daytime nap affording an intermediate benefit (*i.e.,* sleep > nap > wake). As hypothesized, the sleep and nap groups improved significantly more than the wake group. However, surprisingly, the nap group demonstrated significantly greater improvement on speed than the sleep group. It is likely that the shorter time interval between training and retest in the nap group may explain the significantly greater behavioural improvement in speed in the nap *vs.* sleep condition.

2.2. Consolidation can still benefit from wake. Memory consolidation optimally occurs when a period of practice is followed by a period of sleep, particularly when compared to a period of wakefulness (Fogel et al., 2015; Walker et al., 2002). However, that is not to suggest that consolidation occurs exclusively during sleep, and recent work has suggested that a period of quiet rest affords the same benefit of consolidation as a period of sleep (Craig et al., 2018; Humiston & Wamsley, 2018). Importantly, behavioural results from this thesis demonstrated that the wake

group still improved on the task (*i.e.,* all groups still improved after their interval, and there was no detriment to task performance at retest for any of the sleep, nap, or wake groups). Despite behavioural improvements on the ToH following an offline interval of sleep, nap, or wake, our results suggest that memory consolidation benefits more from post-learning sleep (either a nap or night of sleep), and that a full night of sleep is necessary for optimal consolidation of the memory trace to occur at the neural systems level.

2.3. Is a nap as good as a night of sleep for procedural memory consolidation for cognitive strategies and problem-solving skills? A daytime nap has afforded the same benefits as a full night of sleep, specifically for other procedural tasks such as texture discrimination (Mednick et al., 2003). Only a handful of studies (Doyon et al., 2009; Sugawara et al., 2017; van Schalkwijk et al., 2017) have directly compared the benefit of a full night of sleep to a daytime nap for memory consolidation. Doyon et al. (2009) observed that motor sequence learning improvements were similar between sleep and nap, but both were advantageous as compared to a period of wake. By contrast, visuomotor adaptation showed improvement regardless of whether a night of sleep, a daytime nap, or day of wakefulness took place during the consolidation interval. Van Schalkwijk et al. (2019) observed wake-related deterioration on procedural mirror tracing and on declarative memory for word-pairs. In addition, stabilization was observed following a daytime nap, and improvement was observed following sleep but for declarative memory only. Other work has shown that a daytime nap and a full night of sleep led to improved motor sequence performance, however only a full night of sleep led to fewer errors and greater activity in the putamen (Sugawara et al., 2017). The present studies reveal a generally similar pattern for behavioural improvement, and further suggest that a full night of sleep is optimal over nap and wake for the memory trace to be consolidated, as shown through strengthened activation of the

hippocampus, striatum, and neocortex. This pattern of results supports our hypothesis that sleep > nap > wake at the neural systems level for cognitive strategies and problem-solving skills.

3. The Role of REM Sleep in Consolidating Memory for Cognitive Strategies and Problem-Solving Skills.

3.1. The paradox of REM sleep. REM sleep was first identified in humans for its characteristic eye movement bursts (Aserinsky & Kleitman, 1953), and was simultaneously identified in cats by Michel Jouvet (1959), who termed this state '*sommeil paradoxal'* due to its paradoxical combination of wake-like neural activity during a deep sleep period of non-responsiveness. Indeed, functional connectivity networks during REM sleep are closer to the wake state than during NREM sleep (Houldin et al., 2021), and there are no unique functional networks in REM sleep (Houldin et al., 2019). The paradox of REM sleep extends to its respective phasic and tonic microstates: in phasic REM sleep, the sleeping brain and oculomotor activity is most active, yet this is also when the brain is less likely to react to external stimuli as compared to tonic REM sleep, which is characterized by the absence of rapid eye movements (Miyauchi et al., 2009; Wehrle et al., 2007).

REM sleep has been identified as an opportune time to focus inwards, possibly to replay information (Klinzing et al., 2019) and rebalance synaptic plasticity from the day before (Tononi & Cirelli, 2014). In *Study 1* of this thesis, theta was not only time-locked to rapid eye movements during phasic REM sleep, but was also correlated with behavioural improvements. Future studies (*e.g.*, in animal models) are needed to investigate the precise nature of how theta time-locked to rapid eye movements is involved in systems and cellular level memory consolidation. For example, by investigating memory replay during REM sleep.

3.2. The memory function of REM sleep theta activity. Similar to the REM paradox, a 'theta paradox' has been proposed, as theta activity occurs both during drowsiness from sleep

deprivation, and during alert cognitive control (Snipes et al., 2022).Unlike NREM sleep, theta activity in the PFC is similar between REM sleep and waking (Buzsaki, 2002; Montgomery et al., 2008). Given that the majority of REM sleep occurs when the subjective need for sleep (*i.e.,* homeostatic sleep pressure) is lowest (Bes et al., 1996; Borbely, 1982), it is unlikely that REM theta has a recovery function from sleep pressure. Rather, REM theta might reflect a protected, inward-focused time for cognitive processing; a wake-like state, but without external sensory input.

3.3. The underexamined role of phasic and tonic REM sleep. Findings from *Study 1* demonstrated that theta power time-locked to rapid eye movements was increased following learning *vs*. a control night, and, this increase in theta power was positively correlated with performance improvements. Increased rapid eye movements have been observed following intensive language learning (De Koninck et al., 1989; Hébert & De Koninck, 1994) and schema-conformant processing (Durrant et al., 2015). Previously, increased theta power has been observed during REM sleep following new learning (Durrant et al., 2015; Picard-Deland et al., 2021; Thompson et al., 2021), but only recently linked to phasic REM sleep (Picard-Deland et al., 2021) or time-locked to phasic rapid eye movements themselves (Thompson et al., 2021).

Very few studies have investigated the role of tonic REM sleep for memory consolidation. The available evidence has shown that the duration of tonic REM sleep is linked to overnight improvement for gross-motor skills (*i.e.,* inverse bicycle riding; Bothe et al., 2019). As we observed during *Study 1*, not only were theta and SMR power greater on the ToH learning night compared to the non-learning control nights during both phasic and tonic REM sleep, but there were also dissociable processes between phasic and tonic REM sleep: theta and SMR power was greater during phasic REM sleep *vs.* tonic REM sleep, and both theta and SMR power during

phasic REM sleep was correlated with overnight behavioural performance improvement. Next, SMR power during tonic REM sleep increased and even surpassed SMR phasic REM sleep from the non-learning control night to the ToH learning night, whereas SMR power during phasic REM sleep remained stable across nights. These results suggest that phasic and tonic REM sleep are both differentially involved in the consolidation of procedural memory for cognitive strategies and problem-solving skills, possibly to consolidate distinct aspects (*e.g.*, cognitive processing and sensorimotor components) of the memory trace.

The distinctions between phasic and tonic states observed in *Study 1* might partially account for the controversy surrounding the role of REM sleep for memory consolidation. Indeed, the supporting evidence for the *Dual-Process Hypothesis* (Plihal & Born, 1997) may have overlooked not only the multifaceted nature of declarative and procedural memory types, but also the heterogeneity of REM sleep. Considering REM sleep as a unitary state is likely an oversimplification of this still mysterious state, and may overlook whether and how REM sleep is implicated in various forms of memory consolidation. Future studies should continue to examine phasic and tonic REM sleep separately, particularly by focusing more directly on the accompanying brain activity to better understand the functional significance of REM sleep for memory consolidation (and other REM-related phenomena such as dreaming). In summary, findings from *Study 1* advance knowledge on the unique contributions of phasic and tonic REM sleep to memory consolidation: Phasic REM sleep might prioritize consolidation of memory for a cognitive strategy marked by increased theta activity. By contrast, tonic REM sleep may be preferentially involved in processing sensorimotor components of the procedural memory.

4. Hippocampal-Striatal-Cortical Brain Areas and Theories of Memory Consolidation

4.1. Neural substrates of memory consolidation. *Study* 2 and *Study 3* focused on the involvement of the hippocampal-striatal-cortical network of brain areas in sleep-dependent

memory consolidation The findings demonstrate that: 1) the hippocampus is involved in procedural memory consolidation for cognitive strategies and problem-solving skills, 2) the caudate is preferentially involved in sleep-dependent procedural memory consolidation for cognitive strategies and problem-solving skills, and 3) functional connectivity is strengthened between the hippocampus and orbitofrontal cortex following a consolidation period of sleep. These changes are strongest when the consolidation interval contains sleep *vs.* wake.

The role of the striatum is functionally dissociable from the hippocampus during procedural memory consolidation (Albouy et al., 2008, 2012, 2015; Albouy, King, et al., 2013; Albouy, Sterpenich, et al., 2013). The putamen is recruited during motor skills learning, and is strengthened after a period of sleep *vs.* wake (Debas et al., 2010; Fogel et al., 2017). *Study 2* demonstrated that for problem-solving skills, the caudate is the striatal component that is recruited during learning and strengthened after a period of sleep. Thus, this thesis extends behavioural work that sleep preferentially consolidates procedural memory for cognitive strategies, showing domain-specific recruitment and sleep-dependent consolidation processes that are distinct from memory consolidation for cognitively simple procedural motor skills.

4.2. Theories of Memory Consolidation. In *Study 2*, the observed decrease in hippocampal activity and increase in neocortical activity after a period of sleep (*vs.* nap and *vs.* wake), are in line with the Active Systems Consolidation model of memory consolidation (McClelland et al., 1995; Squire & Alvarez, 1995), and further suggest that sleep facilitates the hippocampal-neocortical transfer of the memory trace.

A complementary hypothesis is the Multiple Trace Theory (Nadel & Moscovitch, 2001; Rosenbaum et al., 2001), which posits that, upon initial acquisition, multiple traces are formed in domain-specific brain areas, all of which independently process aspects of the memory.

Additionally, the hippocampus may remain involved after consolidation for memories that are contextually rich or episodic in nature. Our findings from *Study 2* are consistent with Multiple Trace Theory in that distinct domain-specific brain regions were associated with improvements in behavioural performance. In addition, the results from *Study 3* show that functional connectivity between these domain-specific brain areas is strengthened following a consolidation period of sleep *vs.* wake (*e.g.,* hippocampal-OFC and caudate-somatosensory cortex). Taken together, these results provide complementary support for both the hippocampal-cortical transfer hypothesis and Multiple Trace Theory. More specifically, the hippocampus might be a central hub for initial acquisition of the memory trace (especially in terms of the spatial aspects of the memory), and will preferentially transfer/integrate this information into the neocortex (*e.g*., sensorimotor, frontal and other association areas) during the subsequent sleep opportunity. Activation and functional communication between domain-specific areas (*e.g.,* caudate, OFC) that are specifically involved in cognitive strategies may be involved in the long-term storage and retrieval of the memory trace.

5. Consistent Findings Across *Study 1*, *Study 2*, and *Study 3*

Considering findings from *Study 1*, *2*, and *3* altogether, the EEG and fMRI results show at least three consistent patterns worth mentioning. First, increased (ToH *vs*. Control night) theta activity over prefrontal scalp areas during REM sleep, increased activation in multiple frontal/prefrontal neocortical areas following sleep (compared to wake), and strengthened hippocampal-OFC functional connectivity following sleep (compared to wake), were all positively correlated with sleep-dependent behavioural improvements. The relationship between behavioural improvements and systems-level functional communication in domain-specific brain areas provide compelling evidence to support the notion that sleep plays an active role in memory consolidation.

Second, increased SMR (ToH *vs*. Control nights) during tonic REM sleep, and strengthened functional connectivity between the caudate and SMA's somatosensory area

following a consolidation period of sleep *vs.* wake, both support a role for sleep in the enhancement of sensorimotor function. These findings are consistent with previous findings of brain areas involved in mental imagery, associative sensorimotor learning (Lehéricy et al., 2005), and with automizing implicitly learned information (Destrebecqz et al., 2005; Peigneux et al., 2000), all of which are skills needed for procedural problem solving. These parallel findings suggest that theta power during tonic REM sleep might reflect processing from sensorimotor-related neuroanatomical substrates (*e.g.,* the caudate and somatosensory cortex).

Finally, it has been hypothesized that the PFC orchestrates communication between the hippocampus and the striatum to consolidate procedural memory traces (Albouy et al., 2015; Albouy, Sterpenich, et al., 2013). Not only are the striatum and OFC structurally connected to one another (Haber et al., 1995), but findings from *Study 3* show that functional connectivity between the hippocampus and OFC is strengthened following a consolidation period of sleep (*vs.* wake), and that the extent of this is positively correlated with improved performance. In general, the neocortex is less active during REM sleep compared to NREM3 and wakefulness, however, the OFC and dlPFC are two exceptions, which show increased activity during REM sleep compared to NREM3 (Braun et al., 1997) and wakefulness (Nofzinger et al., 1997). Moreover, beta power in the OFC is stronger during REM sleep compared to NREM sleep, and specifically, strongest during phasic REM sleep than tonic REM sleep (Nishida et al., 2005). Thus, it is possible that for types of memory that are heavily dependent on the prefrontal cortex (such as problem-solving skills), phasic REM sleep may be uniquely involved/required for this form of sleep-dependent memory consolidation. Our observations of increased theta over prefrontal scalp areas time-locked to phasic REM sleep (compared to a non-learning control night), alongside increased hippocampal-

OFC functional connectivity, suggest that REM sleep and the PFC are important for the consolidation of problem-solving skills.

6. Memory Types

Although procedural memory requires motor sequence execution, an important subset of procedural skills involve rule-learning and the acquisition of cognitive strategies. Sleep appears to be distinctly involved in the consolidation of these forms of memory. Before examining procedural memory for cognitive strategies at the neural systems level, work from our group (van den Berg et al., 2019) and others (Conte et al., 2020) have shown how sleep, to optimally consolidate memory, distinguishes between the several processes which accompany procedural memory. In both cases, these studies show that, rather than consolidating the traditionally non-declarative simple procedural motor skills, sleep preferentially enhanced memory for the cognitive strategy.

This distinction between cognitive strategies and simple motor skills within the procedural memory domain was elucidated in the field of sleep and memory research, particularly as sleep seemed to present an additional dissociation within the domain of procedural memory (Smith, 2001). Specifically, Carlyle Smith defined these constructs as *cognitive procedural memory*, in contrast to *simple procedural memory* (Smith, Aubrey, et al., 2004). The repetitive, simple motor sequence performance (*i.e.,* simple procedural memory) benefitted from NREM sleep, whereas any 'cognitive procedural' memory component that accompanied the motor movements – including cognitive strategies and problem-solving skills – benefitted from REM sleep. The findings of this thesis are consistent with Smith's studies of cognitive procedural memory.

7. Limitations and Future Directions

7.1. Multimodal imaging using simultaneous EEG and fMRI. EEG and fMRI were not recorded concurrently in the present studies. However, the findings from this thesis lay down important groundwork for such studies, which could focus specifically on memory trace

reactivation during sleep. Future studies employing simultaneous EEG-fMRI – during both task performance and during sleep – can leverage the high temporal resolution of EEG in combination with the high spatial resolution and coverage of MRI. This has been done for studies investigating the memory trace reactivation time-locked to sleep spindles for simple procedural motor skills, whereby NREM sleep spindles time-locked to the putamen are associated with overnight motor sequence improvement (Boutin et al., 2018; Fogel et al., 2017). An analogous process might occur for improvement on procedural memory for cognitive strategies and problem-solving skills, whereby: 1) reactivation of brain areas involved in the acquisition of cognitive strategies and problem solving (*e.g.,* hippocampus, caudate, prefrontal cortex) may be time-locked to phasic REM sleep, and, 2) periods of tonic REM sleep might be similarly linked to increased caudate-somatosensory functional connectivity.

7.2. REM Sleep and Daytime Naps. The presence or absence of REM sleep during a daytime nap appears to be a key predictor of improved performance. For example, previous studies have shown that nappers who experienced REM sleep after performing a perceptual texture discrimination task showed evidence for consolidation upon awakening, compared to nappers who did not experience REM sleep (McDevitt et al., 2015). Furthermore, the degree of improvement was proportional to the increased amount of REM sleep (McDevitt et al., 2015). However, naps do not consistently contain REM sleep. In the present study, despite a 90-minute nap opportunity, only n=15 participants reached REM sleep, and those that did had only a very short period (M=8.23, SD=*4.7* minutes). This precluded any meaningful detailed analysis of the REM sleep data, particularly if further dividing REM sleep into phasic and tonic REM sleep. Future studies between sleep and nap could benefit from either extended daytime sleep periods, or early morning REM sleep restriction the night before to ensure sufficient REM sleep is achieved.

7.3. How NREM sleep might consolidate procedural memory for cognitive strategies and problem-solving skills. In the present study, we assessed memory consolidation for the ToH task. The ToH and related tasks are classically associated with increases in REM sleep (Brand et al., 2010; De Koninck & Prevost, 1991; Fogel et al., 2015; Smith, 1995; Smith, Nixon, et al., 2004). Nevertheless, other findings suggest that the ToH may not be a purely REM-dependent task. For example, spindle density and the percentage of time spent in NREM2 sleep (Nielsen et al., 2015), as well as the amplitude and duration of NREM sleep spindles (Fogel et al., 2015), have also been associated with consolidation of memory for the ToH. REM sleep and NREM sleep are therefore involved in dissociable aspects of consolidating procedural memory for cognitive strategies and problem-solving skills.

It is possible that REM sleep preferentially consolidates memory for the novel cognitive strategy, while NREM sleep is responsible for the fine-tuning of existing skills (Smith, Aubrey, et al., 2004). Indeed, Fogel et al. (2015) observed an effect of REM sleep on consolidation for the ToH immediately after initial learning (when the cognitive strategy is novel), whereas NREM sleep spindles were implicated a few days after with further extensive practice – when the strategy had been mastered, and the task execution was well-learned. Similarly, Nielsen et al. (2015) observed that the percent and time spent in NREM2 were greater in those who improved on the ToH compared to those who did not improve, and, spindle density was specifically correlated with speed rather than number of moves, thus supporting the classic role of NREM sleep spindles for speed execution of simple motor sequences (Barakat et al., 2012; Fogel et al., 2007; Fogel & Smith, 2006; Morin et al., 2008; Nishida & Walker, 2007).

The differentiation between REM sleep and NREM sleep has also been reflected in dream content after performing a gross-motor procedural skills task: Reintroduction of a task-relevant

auditory cue during REM sleep evokes task-related dream content only if cued 1-2 days after initial learning, whereas cues occurring during NREM3 sleep evoke task-related dream content 5-6 days after initial learning (Picard-Deland & Nielsen, 2022). Together, these studies implicate a role of REM sleep for newly acquired and cognitively demanding procedural memories, and a role of NREM sleep in fine-tuning of the existing skills and improvement on motor speed. This is complementary to Smith et al.'s (2004) emphasis on REM sleep being implicated when the procedural task is difficult *vs.* NREM sleep being implicated when the procedural task is less cognitive demanding (see section ***6. Memory Types***). Future studies on procedural memory for cognitive strategies and problem-solving could consider the trait-like cognitive abilities of participants. Indeed, individuals who quickly master the task prior to sleep might rely more on the fine-tuning benefit of NREM sleep, compared to those who have not yet mastered the problem during wake who might benefit from REM sleep. However, it should be noted that these types of tasks typically require a considerable amount of practice over multiple sessions. Furthermore, an assessment after several days and nights of alternating practice and sleep might provide additional insight into the dissociable roles of NREM and REM sleep for procedural memory consolidation (see Fogel et al 2015).

7.4. Implications for Sleep-Related Memory Consolidation and Aging. The present studies focused only on healthy, young adults. However, both sleep and memory change with age, and previous studies have identified that while healthy older adults learn procedural motor sequences at the same rate as young adults, they lose the benefit of sleep for memory consolidation (Fogel, Albouy, Vien, et al., 2014; King et al., 2013). Several age-related changes in sleep architecture have been suggested as neural markers of the reduced benefit of sleep for memory consolidation, including slow waves (Carrier et al., 2011), sleep spindles (Fogel, Albouy, Vien, et

al., 2014; Fogel et al., 2012; Martin et al., 2012), and uncoupling of spindle-slow waves (Helfrich et al., 2018). Furthermore, age-related reductions in both sleep spindles and putamen activity contribute to observed deficits in procedural memory consolidation for older adults compared to young adults (Fogel, Albouy, Vien, et al., 2014).

Recent work from our group has shown that the age-related reduced benefit of sleep for memory consolidation extends to memory for cognitive strategies and problem-solving skills (Toor et al., 2022; 2023). Specifically, reduced sleep-related gains in performance on the ToH is also reflected by reduced hippocampal-cortical transfer of the memory trace compared to young adults, following a daytime nap (Toor et al., 2022). Furthermore, not only are age-related reductions in grey matter intensity observed within the hippocampal-striatal-cortical network of brain areas, but grey matter is differentially correlated with NREM oscillations (*e.g.*, sleep spindles, slow waves) and with sleep-dependent gains in ToH improvement, whereby young adults show a positive correlation and older adults show a negative correlation (Toor et al., 2023).

Future studies can continue to build on findings from the present thesis to further understand the relationship between age-related impairments to sleep quality and memory consolidation. For example, it is likely that older adults show weakened functional connectivity compared to young adults following a consolidation period of sleep. Finally, a similar approach could be used to investigate if EEG time-locked to rapid eye movements in young adults differs with age in older adults, and the associated impact on sleep-dependent memory consolidation.

8. Conclusion

Some of the most important discoveries have been realised following a period of sleep. The headmaster at the Jesuit College permitted René Descartes to sleep in on school day mornings (Wollaston, 1964) – thus providing extra time when REM sleep is most prominent – and this is

consistent with the anecdote that Descartes realised the necessity of the scientific method (Baillet, 1691; cited in Feuer, 1963; Withers, 2008 in his sleep.

The findings from this thesis show that memory consolidation for cognitive strategies and problem-solving skills is preferentially enhanced by sleep, and specifically, by dissociable roles of theta and SMR during phasic and tonic REM sleep. This consolidation process is reflected by sleep-dependent increased recruitment of the caudate and domain-specific regions of the neocortex, along with decreased recruitment of the hippocampus over time. The extent of these changes is associated with offline gains in performance. Moreover, we found that sleep strengthens resting-state functional communication between brain areas involved in the consolidation of problem-solving skills, and, the extent of this increased functional connectivity was associated with performance improvements. While a daytime nap appears to afford some benefit at the behavioural level, a full night of sleep is required for systems-level consolidation of memory traces for procedural cognitive strategies and problem-solving skills.

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Appendix A. Consent Form.

INFORMATION SHEET AND CONSENT FORM

Project: Neural Correlates of Cognitive Procedural Memory Consolidation During Sleep

Principal Investigator: Stuart Fogel, Associate Professor, School of Psychology, University of Ottawa, 613-562-5800 ext 4295, sfogel@uottawa.ca

Thank you for your interest in this study. Before you decide whether to take part, please read the following information carefully (this sheet is for you to keep). You may ask us any questions if you would like more information.

What is this research's goal?

We are interested in how young adults learn new cognitive and motor skills. In this experiment, we investigate the brain activity related with learning a task that will require a type of memory called "cognitive procedural memory". Cognitive procedural memory helps you learn new logical strategies and perform skills. Brain activity will be recorded using electroencephalography (EEG) and functional magnetic resonance imaging (fMRI) at the Royal Ottawa Mental Health Center (ROH) Brain Imaging Centre.

Do I have to take part?

It is up to you to decide to join the study. We will describe the study and go through this information sheet. If you agree to take part, we will then ask you to sign a consent form.

You are free to withdraw at any time, without giving a reason. You can skip any questions you do not wish to answer (except for the MRI safety checklist, which is required in order to ensure your safety).

What will happen if I agree to take part?

If you decide to take part, you will be asked to come to the ROH Sleep Research Laboratory three separate times, including one, two or three nights (depending on the group you are randomly assigned to). If you agree to take part and sign the consent form, we will first ask you to complete a series of questionnaires. On two occasions you will have an fMRI scan, which will take place in Brain Imaging Center at the ROH, to record your brain activity while you complete a task in the scanner. Depending on the group that you are assigned to, you might be asked to either spend an additional night sleeping in the laboratory, you will be asked to take a nap for 2.5 hours during the day, continue throughout the day without sleeping. Following these sessions, you will then complete the same task a second time.

For the fMRI sessions, you will lie in a narrow tube in the fMRI scanner and hold still for approximately an hour, and no longer than 1.5 hours. It may not be appropriate for you to be scanned if you are very claustrophobic. Because the scanner itself is quite noisy, we will give you earplugs to protect you from that noise. Throughout the experiment you will be in direct verbal communication with us. We can terminate the experiment at any point should you experience any discomfort or distress. You can also request breaks whenever you need one. In

the scanner, you will complete a memory task using a keypad. You will be asked to complete the task by pressing buttons. The task may be cognitively demanding, but will not be physically tiring. In addition, before you go into the scanner, you will be asked to fill out a safety questionnaire, as well as a questionnaire about sleep quality and mood.

During your nights (~10 hours each) in the sleep laboratory, you will sleep with electrodes on your scalp and face. The placement of electrodes on the head is not painful, although there may be minor discomfort when the skin is cleaned during electrode application. The skin may be slightly reddened after the electrodes are removed. This reddening is normal and will disappear in less than an hour. The electrode gel dissolves in water; and in the morning, you will be able to take a shower after the electrodes have been removed. One of the nights in the sleep laboratory will also include sensors designed to monitor your breathing, limb movements, and oxygen level.

Compensation

You will be compensated for your time and offered free parking at the ROH. Breakfast and toiletries will also be made available on site.

If you choose to withdraw before completing the full study, you will be compensated on a per session basis as follows:

-(a) **$20** for the orientation and screening/acclimatization session,

-(b) **$40** for completing the baseline MRI, EEG session following the initial screening/acclimatization session ($20 for orientation + $20),

-(c) **$70** for attending one experimental session ($20 for (a) + $20 for (b) + $30)

-(d) **$100** for attending study completion, debriefing, and returning logs and activity monitors ($20 for (a) + $20 for (b) + $30 for (c) + $30)

Am I eligible to take part?

To be eligible to take part in this study, you must ***fulfill the following criteria***:

- 20 to 35 years of age
- fluent in English
- right-handed
- normal or corrected-to-normal vision
- a normal sleep schedule (e.g., sleep between the hours of 10pm and 9am)
- in good health
- have a normal body mass index
- non-smoker
- non-professional typist or musician
- do not consume excessive caffeine or alcohol
- non-shift worker

And have no:

- sleep disorders
- neurological and/or psychiatric disorders (past and present)
- loss of consciousness for more than 10 minutes at any point in the past (other than under anaesthesia)
- metal in body (e.g., piercings that cannot be removed, shrapnel etc.)
- implanted devices (e.g., cardiac pacemakers, aneurysm clips, cochlear implants, medical pumps, deep brain stimulators, etc.)
- back problems
- hand or finger mobility problems

Note: Jewels, body piercings and any clothing with metal will need to be removed if you choose to take part in this study.

And not be:

- pregnant
- claustrophobic
- taking any medications known to interfere with sleep

What sort of data will be collected in this study?

We will collect simple demographic data concerning your age, gender, handedness, first language, years of education, vision, and self-reported medical history. We will also collect your evaluation of your sleep quality, your mood, and your sleep preferences.

We will also collect data regarding your task performance.

Additionally, we will obtain several types of brain imaging data, which includes an anatomical picture of your brain and a series of images that will show us your brain activity while you engage in the tasks.

We will also collect EEG data during sleep, which is a harmless and non-invasive way to record the electrical activity of your brain via electrodes placed on the surface of your skin.

What is EEG?

Electroencephalography or “EEG” is a non-invasive technique that measures brain activation. EEG records brain waves through electrodes, which are small metal disks placed in direct contact with the skin. When your neurons communicate with each other, they send a bust of electricity that is picked up by the electrodes. A connected recording machine will measure the strength and duration of the electrical impulse for each brain region close to an electrode. The machine will transcribe those measures into a visual signal that can be traced on a computer screen. Your brain activity will be recorded continuously; this creates a pattern of brain activity on the screen that looks like a series of peaks and valleys, or waves. Depending on what your brain is doing, your brain waves will change as different parts of your brain become more or less activated. We will track those changes on the EEG recording to see how your brain activates while you sleep.

What is MRI?

Magnetic resonance imaging or "fMRI" is a safe and non-invasive technique. MRI does not use x-rays (such as in coaxial tomography or "CAT scans") or ionizing radiation (such as in positron emission tomography, or "PET scans").

MRI is a brain imaging technique that allows us to obtain a 3D picture of your brain using magnetic fields. Our bodies (and brains) are largely made up of water molecules (H_2O), which consist of oxygen (O) and hydrogen (H) atoms. Within the hydrogen atoms, there is a small particle called a proton. Protons act like tiny magnets. Therefore, when you lie in the strong magnetic field of the scanner, these protons will line up with the magnetic field. Then, the scanner produces short bursts of radio waves, which knock the protons out of alignment. Once the radio waves stop, the protons will realign with the magnetic field by which they send radio signals back to the scanner. The scanner feeds them back to our computer, which produces an image based on the exact location of the protons. This information can be used to create a structural image of the brain.

Functional MRI (fMRI) also records blood flow in certain regions, providing us with an indirect measure of brain activity, because we assume that more blood is needed in areas that are activated. Together with structural image, we can then look at the parts of the brain that were activated during the tasks. Please note that, depending on the group you are assigned to, you may go into a "mock scanner" instead of a functioning MRI machine.

What are the possible disadvantages and risks of taking part?

The main disadvantage is that participating will take up some of your time. EEG and MRI are safe techniques, and we will make sure that it is safe for you to go into the MRI scanner. Moreover, you can also choose to skip any questions if you feel uncomfortable with providing an answer (except on the MRI safety questionnaire, for your own safety).

MRI scans are sometimes considered to contain some identifying information given that we could reconstruct some facial features (i.e. the shape of the head). This poses a minimal risk to preserving the anonymity of your data, even if we will associate a numerical code to your MRI scans rather than your name. Only members of the research team will have access to the scans, and they will be kept securely as described in the section beginning with: "**How will you store the information that I give you?"**. EEG data does not contain identifying information, and will also be associated with a numerical code so that your data remains anonymous.

You will lie in an MRI tube for about one hour at a time. For that reason, you should not participate in this study if you are claustrophobic or if you have back problems. The scanner is loud. We will provide you will ear plugs to ensure that the noise is kept to a safe level.

You will wear the EEG electrodes during the night. This may be slightly uncomfortable or annoying, but should not interfere with your sleep through the night. Electrodes only record electrical signals of the brain, so you will not receive any electrical charge or impulse.

Lastly, the MRI scan may detect anomalies that neither you nor your doctor(s) were expecting. This is known as an Incidental Finding (see below).

Incidental Findings

If the technologist is unsure about the scan, your scan may be looked at by a Consultant Radiologist. From other published studies we know that in a small proportion of participants (about 2.5%) worrying incidental findings may occur. These results from incidental findings in young healthy volunteers are often benign, but either way, this is a good thing to know, as we may detect something that your doctor should know about at an early stage.

If this happens, a health professional of the ROH will contact you by telephone and explain these findings. All information will be made fully available to you. They will arrange the necessary next steps with you. This includes contacting your family doctor and, if appropriate, referral to a specialist for further tests.

However, this is not a diagnostic scan and we are not conducting medical research, nor are researchers trained physicians or health professionals, and therefore, there is no guarantee existing anomalies will be detected. If you prefer not to be informed of an image anomaly, you must choose not to participate in the study.

What are the possible benefits of taking part?

If you are interested in learning about the importance of sleep, about the brain and about how MRI and EEG work, this is a great opportunity to learn. Your participation will benefit the program of research and our knowledge about the function of sleep.

We cannot provide personal feedback on any of the tasks, because we are not clinicians and because the tasks are performed to satisfy research purposes. The tasks are intended to be meaningful at the group level, and not at the individual level, and so your individual test results are only meaningful when considered as part of a group.

Will I be paid for taking part in this study?

We will give you $100 to help cover any costs associated with participating and completing this study, and in acknowledgement of the time commitment and potential inconvenience to your schedule we are asking of you.

What will happen if I agree to take part, but change my mind later?

You have the right to withdraw from the study at any time during the experiment (e.g., even during MRI scanning you can press the emergency call button while lying in the MRI scanner and indicate you wish to discontinue the experiment; you can decide to signal the experimenter during the night and ask for the EEG electrodes to be removed).

How will the data be used?

The information obtained from this study will be presented at scientific conferences or in scientific journals, but your name will never appear in any public document. Only group data will be presented.

Your data may also be used in future studies as part of research in the laboratory of Dr. Stuart Fogel for the duration the data will be stored. This data includes personal characteristics, questionnaires, results on cognitive tasks, and fMRI-EEG data. The data will be anonymized, which means a numeric code will be attached to it, and no identifying information will be included (e.g. name, contact information). These data are costly to acquire, and may be useful in future research. Study information may be reviewed by members of the Research Ethics Board for quality assurance purposes.

Will my taking part in this study be kept confidential?

All information we collect about you in this experiment will be kept strictly confidential. Data will be anonymized, i.e., a code will be associated to your data and only group data will be presented. You will not be personally identified in any publications.

How will you store the information that I give you?

Any information about you that is collected during the study will be kept strictly confidential. Only the researchers will have access to this information. All information will be coded so that your identity remains anonymous. The anonymized data will be stored on password-protected hard drives in the Sleep Research Laboratory (Vanier Hall, 3047), in locked filing cabinets in locked rooms, and the Consent Form will be stored in a separate locked room (Vanier Hall, 3040).

How do I know that this research is safe for me to take part in?

All research in the University is looked at by an independent group of people, called a Research Ethics Board, to protect your safety, rights, wellbeing, and dignity. This study has been approved by the Research Ethics Board of ROH March 1st, 2017 and the University of Ottawa (to be specified).

You are under no obligation to agree to take part in this research.

If you do agree you can withdraw at any time without giving a reason.

This study is being supervised by Dr. Stuart Fogel at the School of Psychology, University of Ottawa. If you have any questions or comments on the study, you can contact Dr. Stuart Fogel at 613-562-5800 ext 4295, or sfogel@uottawa.ca . You can contact the Research Ethics Board – Protocol Officer at 550 Cumberland St., Room 154, Ottawa, (613) 562-5387, ethics@uottawa.ca. You may also contact the Chair of Research Ethics Board at the ROH, 1145 Carling Avenue, Ottawa , Ontario, K1Z 7K4; (613) 722-6521 ext 6214.

I confirm that I have read and understand the information sheet for the above study and have had the opportunity to consider the information, ask questions, and have had these answered satisfactorily. ☐

I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. ☐

3. I understand that incidental findings from my MRI scans will be reported to my family doctor. ☐

4. I know that no personal information (such as my name) will be shared outside of the research team or published in the final report(s). ☐

5. I agree to take part in the above study. ☐

One copy is for you to keep, and one is for the researcher. Please sign both.

Participant's name:…….

Participant's signature:…….Date……

Researcher's name……..

Researcher's Signature……Date……

PERMISSION TO BE CONTACTED FOR RESEARCH

The University of Ottawa Institute of Mental Health Research (IMHR) is committed to building a future where we can identify and successfully treat mental illness.

We are asking you for your permission to allow approved research staff to contact you to see if you are interested in participating in a research study being conducted at the IMHR.

Even if you provide your permission to be contacted now, you may withdraw your permission at any time. If you prefer not to be contacted for research, your care and treatment will not be affected in any way.

Any personal health information you may give us is protected under the Personal Health Information Protection Act, 2004 (Ontario).

SIGNATURE FOR FUTURE STUDY CONTACT

- ✓ I understand that studies may want to contact me in the future to see if I am interested in additional study components or other studies I may be suitable for and that I need to provide my permission that approved research staff may contact me. I know that I can change my mind by notifying current study staff and that I can decline future study participation.

- ✓ I will be asked if I want a copy of this permission to contact form to bring home.

I FREELY ACCEPT TO BE CONTACTED IN THE FUTURE ABOUT OTHER STUDY OPPORTUNITIES

Print Name of < Participant/Patient>	Date (to be entered by Participant)	Signature
Print Name of person asking permission to contact for research	Date	Signature

Appendix B. Screening Questionnaire

Today's Date (dd/mm/yy): _____ Time: _____ am / pm

General Questions

1. How old are you?: _____
2. Are you a smoker or non-smoker?: smoker / non-smoker
3. How many caffeinated drinks do you typically have in a day?: _____
4. How many alcoholic drinks do you typically have in a week?: _____
5. Are you right or left handed?: left / right
6. Are you a trained, or professional musician?: yes / no
7. Are you a trained, or professional typist?: yes / no
8. Are you willing and able to abstain from caffeine, nicotine, drugs and alcohol, at least 3 days prior to and throughout participating in this study?: yes / no

Sleep Questions

1. What is your usual bedtime?: _____
2. What is your usual wake time?: _____
3. Are you willing and able to go to bed between 10pm and midnight and wake between 7am and 9am, at least 3 days prior to and throughout participating in this study?: yes / no
4. Do you work nights or shift-work?: yes / no
5. Have you taken a trans-meridian trip (i.e., crossed time zones) in the last month?: yes / no
6. Do you have difficulty falling asleep at night?: yes / no
7. Do you wake up often during the night and are unable to return to sleep?: yes / no
8. Would you describe yourself as excessively tired during the day?: yes / no
9. Have you ever been diagnosed with a sleep disorder?: yes / no
10. Do you know, or has anyone ever told you that you stop breathing while asleep?: yes / no
11. Do you know, or has anyone ever told you that you snore?: yes / no

Health Questions

1. Are you presently in good health?: yes / no
2. Are you pregnant?: yes / no
3. Are you presently taking any medications?: yes / no
4. Do you have a history of chronic pain?: yes / no
5. Do you have a history of anxiety or depression?: yes / no
6. Have you ever suffered any kind of head trauma?: yes / no
7. Have you ever suffered any kind of seizure?: yes / no
8. Have you ever been diagnosed with a neurological or psychiatric condition?:yes/no
9. What is your weight? _____; and your height? _____
   BMI = (Weight in Pounds / (Height in inches x Height in inches)) x 703
   BMI = (Weight in Kilograms / (Height in Meters x Height in Meters))
   BMI [≤25]: _____
10. Do you have any mobility problems with your hands or fingers?: yes / no

Name*: _____
Telephone number(s)*: _____
E-mail*: _____

For Office Use Only

Date of orientation: _____
Dates of recording night: _____
Subject ID: _____