A Dance of Neural Rhythms: Coupling of Slow Oscillations and Spindle Activity During Sleep, in Relation to Memory and Ageing

Oren Weiner

A Thesis

In the Department of

Psychology

Presented in Partial Fulfillment of the Requirements

for the Degree of

Doctor of Philosophy (Psychology)

Concordia University

Montréal, Quebec, Canada

June 2023

CONCORDIA UNIVERSITY
School of Graduate Studies

This is to certify that the thesis prepared

By: **Oren Weiner**

Entitled: **A Dance of Neural Rhythms: Coupling of Slow Oscillations and Spindle Activity During Sleep, in Relation to Memory and Ageing**

and submitted in partial fulfillment of the requirements for the degree of

Doctor of Philosophy (Psychology)

complies with the regulations of the University and meets the accepted standards with respect to originality and quality.

Signed by the final examining committee:

Dr. Elizabeth Teel	Chair
Dr. Ysbrand van der Werf	External Examiner
Dr. Shimon Amir	Examiner
Dr. Karen Li	Examiner
Dr. Natalie Phillips	Examiner
Dr. Thien Thanh Dang-Vu	Thesis Supervisor

Approved by _____
Dr. Andrew Chapman, Graduate Program Director

July 31, 2023 _____
Dr. Pascale Sicotte, Dean, Faculty of Arts and Science

Abstract

A Dance of Neural Rhythms: Coupling of Slow Oscillations and Spindle Activity During Sleep, in Relation to Memory and Ageing

Oren Weiner, Ph.D.

Concordia University, 2023

Sleep undergoes both quantitative and qualitative changes across the lifespan, which accompanies age-related declines in memory. Contemporary research suggests that synchronized cross-frequency coupling (CFC) of slow oscillations (SO) and spindles during sleep is a neural mechanism of overnight memory consolidation, and it has been hypothesized that an age-related "de-coupling" may contribute to memory impairments in older adults. However, evidence for this ageing hypothesis is currently lacking, as most available studies of SO-spindle CFC and memory focus on young adults, with few studies available to directly compare younger and older groups.

The goal of my dissertation is to enhance current thinking about SO-spindle CFC and its relations with ageing and overnight memory consolidation. This work includes two interrelated studies, both examining SO-spindle CFC during sleep in relation to performance on a sleep-dependent declarative memory task. The first study, with 25 healthy seniors, showed that SO-spindle CFC was stable across two recording nights, and that a slow spindle coupling phase closer to the SO up-state predicted better memory consolidation. An exploratory analysis also highlighted potential interactive effects between distinct CFC measures in predicting memory. My second study builds on the analyses from Study 1 with a new sample of 16 older adults compared to 16 young adults, all who completed an expanded 3-night protocol that included a similar memory task and a cognitive control task. This second study showcased age-group differences in coupling during sleep but did not find similarly strong evidence for relations between CFC and memory.

Overall, this work demonstrates 1) a preserved association between certain measures of CFC during sleep and memory in older adults; 2) that coupling dynamics may differ between younger and older adults, but the overall magnitude of coupling may not; and 3) how relations between CFC, ageing, and memory can vary across distinct analytic contexts. Results are discussed in reference to the impact of ageing on brain oscillations and CFC, distinctions in the methods between my two studies as compared to the extant literature, and the impact of even small changes in signal processing decisions on coupling metrics and their association with memory and ageing.

Acknowledgments

First and foremost, I express my appreciation to my research supervisor, Thanh Dang-Vu, for seeing my potential from the beginning, for his guidance and support throughout the process, and for his persistent efforts to push me towards an even greater greatness at each step. I also thank my core thesis committee members, Karen Li and Nathalie Philipps, and my external examiners, Shimon Amir and Ysbrand van der Werf, for their time, expertise, suggestions, and support. This research could not have been completed without the hard work and stamina of the students, interns, and sleep techs in our Sleep, Cognition, and Neuroimaging (SCN) lab, who assisted with recruitment and data collection, and with scoring and analysis steps at various stages of the project. I give special thanks to Jordan O'Byrne, Dylan Smith, Nathan Cross, Aurore Perrault, Florence Pomares, and Melodee Mograss, not only for their individual contributions to this project (big and small), but also for their unwavering support, intellectual stimulation, cheerleading, and encouragement of my personal growth and self-care. Another special thank you goes to the various research coordinators who supported the project and its execution across the years. I further extend my deep gratitude to the volunteer participants who gave their time and efforts to provide data for my research.

I am also thankful for the help and contributions of support staff from the SCN lab, from the PERFORM Centre and the CRIUGM, and from Concordia University. I received generous funding, awards, and scholarships across the years in support of my project, and I give my great thanks for the financial support from Dr. Dang-Vu; from Concordia University's Faculty of Arts and Science and Department of Psychology; from the PERFORM Centre and CRIUGM; Fonds de Recherche du Québec – Santé; and from special research groups within Concordia University, such as the CSBN and engAGE.

My graduate school experience was made ever-more special by the relationships I formed along the way with other clinical students. A very special thank you goes to Jinshia Ly, who – from the start – was my rock and my person in this journey. My experience was further enriched by members of the clinical faculty who provided their wisdom, guidance, and support while in the program; namely, Adam

Radomsky, Dina Giannopoulos, JP Gouin, Lucie Bonneville, and Virginia Penhune, as well as external clinicians: David Sinyor, Debbie Sookman, Jennifer Russell, Nathan Kuperstock, and Wendy Wood.

Last, but certainly not least, I thank my family, who has supported me from behind the scenes since day one, and who relentlessly pushed me to stay on my path towards this goal. I am especially thankful for my partner, Jonathan Hug, who made sure that I was taken care of and loved with each passing day, and through all of the ups and downs of my journey. I dedicate this thesis to all the special people in my life who are still with me now, and to all the ones I love but who are no longer with me.

Contribution of Authors

The studies contained in this thesis were developed from an original research project by a previous graduate student (Jordan O'Byrne), who conceptualized the initial project and overall research program. For both studies included in this thesis, and under guidance of Dr. Thanh Dang-Vu, Oren Weiner developed the specific research questions and analytical directions, constructed the protocol and prepared ethics review documentation, conducted the literature review, developed and/or adapted study materials and stimuli, collected the data (either directly himself, or through supervision of trained research assistants), cleaned and pre-processed the collected data, extracted and analyzed brain oscillation data using specialized programming scripts, conducted the statistical analyses, prepared the tables and figures, interpreted results, and wrote and revised each dissertation chapter. As part of the overall project, Oren also oversaw the hiring and training of undergraduate and graduate student research assistants, as well as organizing and leading PSG recording and sleep scoring workshops for the wider sleep lab team.

As Oren's research supervisor, Dr. Dang-Vu co-developed the research questions, study protocols, analytical directions, and interpretations, and revised dissertation chapters. Brain oscillation analysis scripts, using Python coding software and executed via an in-house analysis program, were developed and refined by Jordan O'Byrne, Dr. Nathan Cross, and Dr. Aurore Perrault. French versions of all study stimuli were developed with the help of French-speaking study coordinators and research assistants.

The manuscripts for Study 1 and Study 2 were both written by Oren Weiner and revised by Dr. Dang-Vu. All listed co-authors in the Study 1 manuscript (now published) contributed to the interpretation of study findings and provided input on the final manuscript.

Table of Contents

List of Figures

STUDY 1

STUDY 2

List of Tables

STUDY 1

STUDY 2

List of Abbreviations

μV……..micro-volts
AASM……American Academy of Sleep Medicine
AHI…….....Apnea-hypopnea index
ANCOVA……Analysis of covariance
B…….....Unstandardized regression coefficient
β……...Standardized regression coefficient
CFC……Cross-frequency coupling
CP……...Absolute coupling phase distance from SO up-state
CRIUGM……..Centre de recherche de l'institut universitaire de gériatrie de Montréal
ECG…….....Electrocardiogram
EMG…….....Electromyogram
EEG…….....Electroencephalography
EOG……...Electro-oculogram
EPSP……Excitatory postsynaptic potential
GABA……....Gamma-aminobutyric acid
HC……...Hippocampus/Hippocampal
hr……..Hour(s)
Hz……....Hertz
IPSP……..Inhibitory postsynaptic potential
med……...Median
MI……Modulation index
MMSE…….....Mini-mental state examination
MoCA……...Montreal Cognitive Assessment
ms……...……...Millisecond(s)
MTL……Medial Temporal Lobe
NREM……Non-rapid-eye-movement
N1……NREM stage 1
N2……NREM stage 2
N3……NREM stage 3
PFC…….....…….Pre-frontal cortex
PGO…….Ponto-geniculo-occipital
PSD……..Power spectral density
PSG…….....Polysomnography
rel_MI……..Relative change in MI between nights
rel_CP……..Relative change in CP between nights
REM……..Rapid-eye-movement
RMS…….....Root mean square
SD……..Standard deviation
SE…….....Standard error
sec……Second(s)
SO……...Slow oscillation
SO(+)……Co-occurring SO-spindle complex
SO(-)……Isolated SO, not joined with a spindle
SO – σ……SO-sigma CFC (with all SO events)
SO(+) – σ……SO-sigma CFC (with co-occurring SO-spindle complexes)
SO(-) – σ……SO-sigma CFC (with isolated SO events)
SWA……..Slow wave activity
SWS……..Slow-wave-sleep
TC……Thalamo-cortical
yr……..Year(s)

A Dance of Neural Rhythms: Coupling of Slow Oscillations and Spindle Activity During Sleep, in Relation to Memory and Ageing

Decades of empirical study has revealed a detailed understanding about sleep from each of it's physiological, behavioural, developmental, phenomenological, and socio-cultural contexts. Further, much is known about relations between sleep and overall physical, cognitive, and mental health (Lemola & Richter, 2012; Reid et al., 2006; Stein et al., 2008), as well as the pathophysiology and consequences of various sleep disorders or deprivation of normal sleep (Desseilles et al., 2008; Goel et al., 2009; Medic et al., 2017; Sigurdson & Ayas, 2007; Tahmasian et al., 2020; Wetter et al., 2010). Despite this, however, the specific reasons for *why* we sleep and why we *need* to sleep are still not fully clear.

Sleep fulfills important adaptive functions, including maintaining bodily homeostasis and thermoregulation, and rejuvenating immune function, contributing to health, and modulating risk of morbidity (Cappuccio et al., 2010; Hall et al., 1998; Weissman et al., 1997). Loss of sleep quality or quantity is also associated with neurocognitive deficits, such as reduced performance on tests of attention and executive functioning (André et al., 2019; Durmer et al., 2005; Olaithe et al., 2018), as well as worsened mental health (e.g., mood and anxiety disorders, suicidality, psychosis; Freeman et al., 2017; Scott et al., 2021; Wang et al., 2019), and difficulties with emotion regulation and stress tolerance (e.g., Åkerstedt, 2006; Deak & Stickgold, 2010; Walker, 2009). Out of all the domains that are impacted or modulated by sleep, there is considerable evidence from a lineage of research in both animals and humans to implicate sleep with overnight memory processing (MacDonald & Cote, 2021; Muehlroth, Rasch, & Werkle-Bergner, 2020; Rauchs et al., 2005; Walker & Stickgold, 2004). Indeed, the sleeping brain, while seemingly at rest, is actively engaged in processing information and consolidating new memories, and in promoting the underlying physiological mechanisms that support neuroplasticity.

The study of memory, and neural mechanisms that support memory, is critical in understanding the general machinery of our own brains. The study of memory also helps us understand how damage to the brain – be it through normal lifespan ageing or through disease or injury – impacts our ability to encode, consolidate, and recall specific memories. Ageing is a natural and universal process that results in

changes (adaptations) to multiple bodily systems and aspects of functioning, including systemic changes, altered regulation of cardiovascular, hormonal, immunological, and metabolic functioning, and changes in neural network activity (Aaron et al., 2022; Kumral et al., 2020). There are multiple theories of biological ageing, such as those based on programmed changes or the result of long-term damage (e.g., wear-and-tear, impact of oxidative stress) (Jin, 2020; Mitteldorf, 2010; Viña et al., 2007). Chiefly, ageing coincides with deficits in cognitive functioning (Deary et al., 2009; Rabbitt et al., 2008; Zaninotto et al., 2018), and in particular with difficulties in forming and consolidating new memories. Accompanying these ageing-related declines in memory are ageing-related declines in sleep quality and quantity (see below), and it has long been considered that the factors of sleep, ageing, and memory are strongly interconnected.

A growing theory posits that neural oscillation activity during non-rapid-eye-movement (NREM) sleep directly supports the processes of sleep-associated memory consolidation, and that natural ageing-related declines in sleep oscillation activity correlate with memory deficits. As will be outlined below, there is a wealth of evidence for the memory-associated functions of cardinal NREM sleep oscillations, such as cortical slow oscillations and thalamo-cortical sleep spindle activity, both of which decline (e.g., in density, amplitude, frequency) with ageing. With developments in theory and methods, attention has pivoted towards investigating the synchronization, or cross-frequency coupling (CFC), between distinct oscillations, which reflects the extent to which activity of one type of brain oscillation (e.g., the phase of a slower rhythm) influences or modulates activity of a separate oscillation (e.g., the amplitude or frequency of a faster rhythm). Multiple studies to-date have reported that precise slow oscillation-to-spindle CFC is related to performance on memory tasks. It is commonly proposed that impaired CFC during NREM sleep with greater age coincides with ageing-related declines in overnight memory consolidation; however, and as will be explained below, there is limited empirical evidence for this hypothesis, due in part to a lack of studies examining CFC and overnight memory consolidation in older adults.

The goal of my dissertation is to build on current thinking about the intersection of sleep and memory in the context of ageing, by conducting a nuanced examination of cross-frequency coupling between brain oscillations during NREM sleep in healthy seniors, and in relation to declarative memory

performance. The two studies in this dissertation focus on non-invasive (scalp-recorded) measures of phase-amplitude CFC. In the following sections, I will provide an overview of sleep and the cardinal oscillations of different sleep stages, which will act as a foundation for the subsequent sections on sleep and associations with memory, where focus is placed on current knowledge about the role of oscillations and CFC in memory consolidation during sleep. I will then draw from available research on sleep and memory in the context of ageing to help contextualize my specific research on NREM coupling and overnight memory consolidation in healthy older adults. Given the wealth of information available about sleep, and relations between sleep and memory, this review will be focused primarily on aspects of NREM sleep (however, see my General Discussion at the end for more about rapid-eye-movement sleep).

Sleep Architecture and Sleep Oscillations

The sleep patterns of typical adults include periods of non-rapid-eye-movement (NREM) and rapid-eye-movement (REM) states that alternate approximately every 90-120 minutes of sleep. NREM sleep is divided into three progressively "deeper" stages (N1, N2, and N3). The pattern and progression of these sleep stages, along with the presence of arousals from sleep during the night, is referred to as sleep "macro-architecture". Sleep progresses from N1, to N2, to N3, and then to REM, with a larger proportion of N3 sleep in the early half of the night and a larger proportion of REM sleep episodes in the later half. Within each sleep stage is a pattern of rhythmic and/or repetitive neural oscillation activity that can be identified and measured, referred to as sleep "micro-architecture" (Davis et al., 1938; Laufs, 2008). The distinct and predictable changes in oscillation activity that occur during sleep can be used to identify the different sleep stages. The following section provides a brief overview of sleep architecture and the cardinal oscillations associated with each sleep stage. See Appendix 1 for an expanded and more complete detailing of these oscillations and their physiological and topographical characteristics.

NREM Sleep

During relaxed wakefulness and the transition to sleep, a sinusoidal alpha rhythm is present (8–13 Hz; 20–40 μV; Constant & Sabourdin, 2012) before entering N1, or light sleep. N1 is characterized by slow eye movements; vertex sharp wave oscillations; and, low amplitude, mixed frequency activity in the

theta range (4–7 Hz; 50–100 μV; Iber et al., 2007; Terzano et al., 2002). N1 is followed by N2 sleep, considered to be stable sleep, and defined by the presence of K-complexes (high-amplitude delta waves, 0.5–3 Hz, typically 100–400 μV and lasting > 0.5 sec) and sleep spindles (Iber et al., 2007; Silber et al., 2007). Sleep spindles (11–16 Hz) are trains of oscillations that wax and wane in amplitude, and last 0.5 to 3 sec (Iber et al., 2007). Spindles can be detected on EEG visually or using event-detection algorithms or measured in terms of spectral power in the "sigma" frequency band. Spindle sequences occur when rhythmic bursts of inhibitory postsynaptic potentials (IPSP) are transmitted from GABAergic thalamic reticular (RE) to glutamatergic thalamo-cortical (TC) neurons; this results in a de-inactivation of a low-threshold Ca^{2+} current that triggers fast Na^{+}-mediated excitatory postsynaptic potentials (EPSPs) across cortical pyramidal networks, which in turn appear as spindle sequences on the EEG (Dang-Vu et al., 2011; Steriade, McCormick, & Sejnowsky, 1993; see also Jensen et al., 2014; Lüthi, 2014; Steriade, 2003; Urakami et al., 2012). Sleep spindles can be further subdivided into slow (< 13 Hz) and fast (> 13 Hz) spindles (Cox et al., 2017), which are prominent across frontal and centro-parietal regions, respectively. The deepest NREM stage is N3, or slow-wave sleep (SWS), which typically dominates the first half of sleep time, and is associated with sleep homeostasis (Dang-Vu et al., 2011). N3 is defined by the presence of delta waves (1–4 Hz, $\geq$ 75 μV) and a cortical slow oscillation (< 1 Hz; > 140 μV) observed in > 20% of an EEG epoch (Iber et al., 2007). SOs occur when large assemblies of cortical neurons collectively vacillate between a depolarized state and a prolonged hyperpolarization phase (Achermann & Borbely, 1997; Steriade, 2001 and 2003). SOs are primarily generated in the neocortex (Amzica & Steriade, 1995; Sanchez-Vives & McCormick, 2000; Steriade, Nunez, & Amzica, 1993a; Timofeev et al., 2000; Timofeev & Steriade, 1996), but have also been detected in the HC (Cox et al., 2020), and may be modulated by the thalamus (Contreras & Steriade, 1995; Steriade, Nunez, & Amzica, 1993b). SO activity is positively correlated with grey matter volume in the medial prefrontal (e.g., orbitofrontal, midline cingulate) cortex (Saletin et al., 2013). Alongside spindles and SOs, sleep coincides with an increase in hippocampal (HC) sharp-wave ripple activity. Ripples, which are most often studied in animals or in patients with epilepsy, have been observed in both the HC and in direct cortical

recordings (Dickey et al., 2021; Khodagholy et al., 2017), and are thought to reflect "offline" neural traces of wakeful experience (Cross et al., 2018; Le Van Quyen et al., 2010; Valderrama et al., 2012). Ripple activity is especially prominent during sleep (e.g., N3), as shown both in mice/rats (e.g., Opalka et al., 2020; Eschenko et al., 2008) and in humans (e.g., Dickey et al., 2021; Staresina et al., 2015).

REM Sleep

REM sleep is characterized by the presence of rapid eye movements (REMs), general muscle atonia, 2–6 Hz "saw tooth" brain waves, ponto-geniculo-occipital (PGO) waves, and low amplitude, mixed frequency activity that resembles relaxed wakefulness or N1 sleep (Iber et al., 2007; McKenna et al., 2017). Prominent oscillatory activity in the theta (e.g., 4–7 Hz) and gamma (e.g., 20–100 Hz) bands is observed during REM in both animals and humans, and in both cortical and subcortical recordings (Bjorness et al., 2018; Brankack et al., 2012; Corsi-Cabrera et al., 2014; Nishida et al., 2004; Penley et al., 2012). REM sleep is divided into tonic (absent REMs) and phasic (present REMs) periods, and there may be distinctions in theta and gamma activity between the two (Simor et al., 2016 and 2020).

Sleep and Associations with Memory

A plethora of research highlights a rich and ever-growing understanding about the relation between sleep and memory (Kroeger & Vetrivelan, 2023; Rauchs et al., 2005; Walker & Stickgold, 2004). Memory consolidation, or the process of strengthening and integrating memory representations into pre-existing networks and schemas (MacDonald & Cote, 2021; Muehlroth, Rasch, & Werkle-Bergner, 2020), has been strongly tied to spontaneous reactivations of memory traces during "offline" periods of sleep, involving coordination of HC (medial temporal lobe; MTL) with frontal and temporal cortical networks (Göldi et al., 2019; Helfrich et al., 2019; Ngo et al., 2020; Schreiner et al., 2018 and 2021). Evidence for relations between better sleep and cognitive functioning comes from studies of subjectively reported sleep (e.g., Wilson et al., 2012) and sleep measured using actigraphy and/or EEG (see below). Further, fMRI-measured HC activity is enhanced during post-learning SWS sleep (Rasch et al., 2007), possibly mediated by reduced cholinergic tone (Gais & Born, 2004). From longitudinal studies, worsening self-reported insomnia symptoms (e.g., difficulties falling asleep, early waking, short sleep

duration) independently predict cognitive decline in older adults (Cricco et al., 2001; Keage et al., 2012; Zhao et al., 2022). However, variability in the samples and designs of these studies contributes to mixed evidence for sleep's role in memory consolidation (c.f., Rauchs et al., 2005). For instance, relations between sleep stages and memory may be modulated by the complexity of the task, level of prior experience/training, type of memory systems activated, and quality of the encoded memory traces (e.g., Cordi & Rasch, 2021; Genzel et al., 2014; Muehlroth et al., 2020), all of which can vary across studies.

Models of Sleep and Memory

Multiple theories of sleep-associated memory consolidation have been developed across the years and continue to evolve. The dual-process theory (see Ackermann & Rasch, 2014, and Rauchs et al., 2005 for reviews) is an early model which posits that NREM and REM sleep have reciprocal roles in overnight memory processing. In the dual-process model, NREM sleep, especially N3, benefits consolidation of HC-dependent declarative (episodic, semantic) memories, while REM sleep strengthens non-declarative memories (e.g., emotional context, skills; Hutchison & Rathore, 2015). However, there is evidence for a role of NREM sleep in procedural learning (Genzel et al., 2009) and of REM sleep in declarative learning (Fogel et al., 2007; see also Stickgold & Walker, 2005). Thus, dual-process models may be too simplistic in arguing for exclusive roles of NREM and REM sleep in consolidating different memories.

Developing from the dual-process model is the sequential hypothesis (e.g., Giuditta, 2014; Giuditta et al., 1995), which posits that recently encoded experiences are initially processed during SWS and further consolidated and integrated into wider networks during subsequent REM sleep. Support, albeit mostly indirect support, for this model is found in studies with animals and humans (e.g., see Ambrosini & Giuditta, 2001 for a review). However, a recent human study (Strauss et al., 2022) showed that, in patients with narcolepsy, spindle activity was related to better visual memory performance only during the normal NREM → REM sleep stage sequence, but not when REM occurred before NREM sleep, as it does in narcolepsy. As well, Tamaki et al. (2020) provided evidence from 4 separate studies that NREM and REM sleep (and the NREM → REM sequence) hold complementary roles in memory processing and consolidation, largely involving different ratios of glutamate to GABA between stages.

The synaptic homeostasis hypothesis (or, SHY model) conceptualizes sleep-associated memory processes as relying on synaptic downscaling. Continuous neural activity during wakefulness causes sustained potentiation of excitatory transmission, expansion of postsynaptic dendritic spines, and the continuous production of proteins involved in synaptic signalling; during sleep, excitatory transmission and dendritic spike volume are downscaled to facilitate synaptic homeostasis, possibly mediated by SWA (McKenna et al., 2017; Nedergaard & Goldman, 2020). Indeed, reduced cortical synaptic strength during sleep is accompanied by decreases in both SO amplitude and slope (c.f., Esser et al., 2007; Riedner et al., 2007; Vyazovskiy et al., 2007). In the context of memory, synaptic downscaling may help to selectively prune weaker synapses (e.g., incomplete/irrelevant memory traces) while retaining the stronger synapses, ultimately increasing the brain's signal-to-noise ratio (MacDonald & Cote, 2021; Tamaki et al., 2020).

Another prominent model of sleep-associated memory consolidation, and the one in focus here, emphasizes the activity and interactions among specific brain oscillations that occur during sleep. In the "active systems consolidation" hypothesis, a "HC-neocortical dialogue" facilitates memory consolidation during sleep via a precise and coordinated interaction of HC ripple, TC spindle, and cortical SO activity (Ackermann & Rasch, 2014; Cairney et al., 2015; Genzel et al., 2014; Geva-Sagiv & Nir, 2019; Rasch & Born, 2013; Todorova & Zugaro, 2020). This model suggests that newly acquired memory traces (or "engrams") in the HC and neocortex are co-reactivated during sleep, and with repeated co-reactivations, alongside precisely timed oscillatory activity, these labile memory traces become consolidated into existing cortical networks and gain independence from the HC (Klinzing et al., 2019). Current thinking emphasizes the role of SO phase as a means of timing cortical synchronization and desynchronization to facilitate information transfer, which itself is largely mediated by coordinated spindle-ripple activity (Helfrich et al., 2019). The following section reviews pertinent evidence for relations between EEG sleep oscillations and memory, with an emphasis on NREM sleep and on declarative/episodic learning paradigms. Oscillations are discussed individually before introducing studies of CFC and memory.

NREM Sleep Oscillations and Overnight Memory Processing

Strong evidence exists for the role of EEG oscillations during NREM sleep in overnight memory processing (see Puentes-Mestril et al., 2019 for a review). A particular emphasis has been given to the study of NREM slow oscillatory activity, including spectral slow wave activity (SWA) and the cortical slow oscillation (SO). EEG spectral power and coherence in the slow (< 1 Hz) and delta (1–4 Hz) bands, among others, during NREM sleep increased following presentation of a word-pair associates task (Mölle et al., 2004), and greater SWA (e.g., 1–4 Hz) is associated with better memory performance in both healthy younger (Holz et al., 2012; Piosczyk et al., 2013) and older adults (Westerberg et al., 2012). Pre-sleep learning may also increase SO up-states and modulate the timing of down-states (Mölle et al., 2009), which in turn can modulate the timing and extent of neural reactivations of memory engrams during sleep (Buzsáki & Draguhn, 2004; Fogel et al., 2012; Jensen et al., 2014; see also Hoffman et al., 2007). As well, experimental induction of SO-like potentials during early NREM sleep via transcranial stimulation enhanced memory retention (Marshall et al., 2006). Together, multiple lines of evidence suggest an important role of NREM SO activity in memory processing. Still, memory encoding and consolidation is also supported by other, faster, NREM oscillations, including spindles and ripples.

Sleep spindle activity contributes to neuronal development (e.g., neuroplastic changes), facilitates sleep maintenance and sleep continuity, and supports memory formation (Astori et al., 2013; Fernandez & Lüthi, 2020; Gais et al., 2002; see also Kumral et al., 2022 for a meta-analysis). Spindle-mediated learning is often attributed to thalamic-reticular burst firing and a spindle-induced influx of Ca^{2+} ions into pyramidal cells across distributed cortical regions that, together, facilitate the growth of dendritic spines and synaptic potentiation (Fernandez & Lüthi, 2020; Ulrich, 2016). Increased spindle activity/density after pre-sleep (declarative or procedural) learning has been positively associated with memory performance in studies using data from all-night sleep (left fronto-central spindles, [Clemens et al., 2005]; bilateral parietal spindles, [Clemens et al., 2006]) and from daytime naps (Ruch et al., 2012; Cairney et al., 2018), and by using measures of sigma spectral power (12–16 Hz; e.g., Holz et al., 2012; Mölle et al., 2004; see also Morin et al., 2008 and Peters et al., 2008). Spindle activity in general may be pertinent to the process of "offline" (or, overnight) memory consolidation, as associations with memory have been

found in examinations of separate N2 (Schabus et al., 2004) and N3 stages (Sopp et al., 2017) and when N2 and N3 are examined together (Gais et al., 2002; Lehmann et al., 2016). Spindle density during post-learning sleep was also correlated with overnight HC-ventromedial pre-frontal functional connectivity, and both were correlated with connectivity during a next-day re-study period (Cowan et al., 2020). Associations with memory become less clear when separating between slow and fast spindles. Relative increases from baseline in both slow (11–13 Hz) and fast (13–16 Hz) spindle activity correlated positively with overnight gains in declarative (word-pair) memory (*r* range = 0.44–0.52; Gruber et al., 2015), while other studies found relations only with fast spindles (van der Helm et al., 2011) or no relation between memory and fast spindle activity (Bar et al., 2020). Similar discrepancies have been found in studies of procedural learning (c.f., Fogel et al., 2007 and Tamaki et al., 2008).

HC sharp-wave ripples during N3 sleep are thought to reflect "offline" neural traces of wakeful experiences (Cross et al., 2018; Eschenko et al., 2008; Le Van Quyen et al., 2010; Valderrama et al., 2012; see also Girardeau & Zugaro, 2011). The hypothesis that HC activity during learning/encoding is "replayed" during post-learning sleep is supported by experimental research in animals (e.g., Girardeau et al., 2009) and in humans (e.g., Axmacher et al., 2008) (see also Fernández-Ruiz et al., 2019; Peyrache et al., 2009; Schreiner & Staudigl, 2020). In line with this, NREM ripple activity has been shown to predict post-sleep memory performance (Zhang et al., 2018), and was more synchronized between HC and cortical recording sites during sleep after learning (Khodagholy et al., 2017), and suppressing ripples via electrical stimulation impaired HC-dependent spatial memory performance in rats (Ego-Stengel & Wilson, 2010; Girardeau et al., 2009). As well, a recent study showed that HC-neocortical connectivity dynamics were especially pronounced during long-duration versus short-duration ripples (Ngo et al., 2020). Taken together, there is strong evidence for a mechanistic role of HC ripples in sleep-associated memory processing, with ripples thought to act as a neural representation of recently encoded experiences that get consolidated during sleep via connectivity between HC and cortical brain regions.

Experimental Interventions on Oscillations during Sleep. The role of sleep oscillations in memory consolidation is further evidenced through experimental studies testing the effects of certain

kinds of external stimulation during post-learning sleep. Such interventions are thought to influence memory consolidation by inducing, enhancing, or otherwise capitalizing on the presence of NREM sleep oscillations. This is shown in studies using transcranial electrical stimulation (Ladenbauer et al., 2017; Marshall et al., 2004 and 2006), auditory stimuli (Harrington et al., 2021; Krugliakova et al., 2020), and rhythmic vestibular stimulation (Perrault et al., 2019). A recent meta-analysis (Barham et al., 2016) demonstrated that transcranial electrical stimulation during sleep had an enhancing or depressing effect on declarative, but not procedural, memory consolidation. However, one study reported no effects of stimulation on declarative memory in younger adults (Bueno-Lopez et al., 2019), and another reported limited or no effects in a sample of older adults (Eggert et al., 2013), suggesting that ageing, and related changes in sleep oscillations, potentially mediates the effect of stimulation on memory.

Targeted memory reactivation (TMR) involves presenting memory-relevant cues or stimuli (e.g., from encoding) to facilitate overnight memory consolidation. Multiple studies provide evidence for a memory-associated benefit of TMR using sensory (e.g., auditory, olfactory) cues during post-learning sleep (e.g., during SWS) (Bar et al., 2020; Cairney et al., 2014; Cox, Hofman et al., 2014; Creery et al., 2015; Schreiner & Rasch, 2015; Schreiner et al., 2015). Memory cues are often timed to a specific phase of the SO (e.g., up-state; Cairney et al., 2018; Göldi et al., 2019; Züst et al., 2019), which could provide an optimal time window for the relative contribution of other sleep oscillations (e.g., spindles; Cairney et al., 2018; Cox, Hofman et al., 2014; Saletin et al., 2011). A recent meta-analysis of 91 experiments (Hu et al., 2020) reported that TMR was more effective at enhancing declarative and skill acquisition memory when cues were presented during NREM sleep compared to during REM sleep or wakefulness.

In sum, correlational and experimental research both provide support for a clear association between brain oscillation activity during sleep and overnight memory processing, and in facilitating learning-dependent neuroplastic changes. Particularly strong associations exist with NREM activity in the SO and spindle frequencies, with more nuanced associations found when examining slow versus fast spindles, and when examining the effect of external stimulation or cueing during post-learning sleep. Thus, learning may be directly reflected in the subsequent activity of brain oscillations during sleep.

Although, it is difficult to reduce the mechanisms underlying such intricate functions to the activity of individual brain rhythms considered in isolation. For instance, Feld and colleagues (2013) argued that pharmacological enhancement of delta activity did not benefit learning performance in their study, possibly due to the medication's additional effect on blunting spindle activity. This result speaks to a potentially salient *interaction* between different brain oscillations in facilitating learning and memory.

Cross-Frequency Coupling of Sleep Oscillations

Cross-frequency coupling (CFC) refers to a statistical interdependence of oscillation activity between slower and faster frequencies, thought to facilitate cognitive processing or optimize neural communication across shorter and longer distances in the brain (Buzsáki, 1996; Buzsáki & de Silva, 2012; Canolty & Knight, 2010; Sullivan et al., 2015; Womelsdorf et al., 2007). Several forms of CFC can be examined, including phase-amplitude, phase-phase, and amplitude-amplitude CFC. The present review is largely focused on studies of phase-amplitude CFC. Phase-amplitude CFC (hereafter referred to just as "CFC") occurs when the phase (e.g., ascending vs. descending) or slope of a slower ("nesting") oscillation is associated with a change in the amplitude of a faster ("nested") oscillation. Various coupling metrics are available, with the most prominent being measures of coupling strength and coupling phase (see Study 1 for more details).

In the following sections I will summarize key contemporary knowledge about CFC between SO and spindle activity during sleep, followed by a review of evidence linking NREM SO – σ (and SO-spindle-ripple) CFC to overnight memory consolidation. Of note, and in most contexts, SO-spindle CFC is also referred to as SO-sigma (σ) CFC, given that CFC analyses are often conducted in relation to spectral power changes. "SO-spindle" (or "SO+spindle") are occasionally reserved for discussions about coupling analyses with overlapping event-detected SO and spindle events. In the context of my thesis, I will refer to this coupling more generally as "SO – σ" CFC, unless otherwise specified.

CFC during NREM Sleep

Phase-coupling of neural oscillations has been widely observed in animals and humans, and there is a growing knowledge base regarding CFC between cardinal NREM oscillations (SO, spindles, ripples).

Coupling dynamics during NREM sleep, mostly between SO and spindle activity, have been examined in studies with animals and in humans, with most human studies comprised of young adult samples (e.g., Cox, van Driel et al., 2014; Klinzing et al., 2016; Mölle et al., 2002, 2004, 2009, 2011; Zhang et al., 2020). A handful of other studies have also described coupling dynamics in samples of children (Hann et al., 2020), middle-aged adults (Abdullah et al., 2015), and older adults (e.g., Helfrich et al., 2018; Ladenbauer et al., 2017 and 2021; Muehlroth et al., 2019). Most studies utilize non-invasive measures of scalp EEG, while others have used magnetoencephalography (MEG; Ayoub et al., 2012) and intracranial or depth electrode recordings (e.g., Clemens et al., 2007 and 2011; Ngo et al., 2020). SO – σ CFC has been examined among healthy participants in a number of studies (e.g., Bartsch et al., 2019; Cairney et al., 2018; Helfrich et al., 2018; Mikutta et al., 2019; Muehlroth et al., 2019; Ruch et al., 2012; Yordanova et al., 2017), and has been examined in patients with schizophrenia (Bartsch et al., 2019; Demanuele et al., 2017), cognitive impairment (e.g., Ladenbauer et al., 2017), Parkinson's disease (Shine et al., 2014; Swann et al., 2015; van Wijk et al., 2016), autism (Mylonas et al., 2021; Kurz et al., 2021), and epilepsy (Amiri et al., 2016; Clemens et al., 2007, 2011; Le Van Quyen et al., 2010; Mak-McCully et al., 2017; Staresina et al., 2015).

Accumulating data suggests there is a typical pattern of CFC during NREM sleep, with faster (centro-parietal) spindles (e.g., 12–16 Hz) peaking around the depolarizing SO up-state, and slower (frontal) spindles (e.g., 9–12 Hz) peaking after the up-state, during the up-to-down-state transition phase (Cox, van Driel et al., 2014; Helfrich et al., 2018; Mölle et al., 2002 and 2011; Muelroth et al., 2019; Niknazar et al., 2015; Staresina et al., 2015). McConnell et al. (2022) recently highlighted a distinction between a frontal slow wave that is coupled to "late-fast" spindles (measured between 10 and 13.5 Hz) mostly during N3 sleep, and a more central slow wave coupled with "early-fast" spindles (measured between 14.6 and 18 Hz) mostly during N2. Coupling of SO and spindle activity may increase with greater sleep depth (e.g., stronger in N3 vs. N2; Cox et al., 2018; Li et al., 2015), and may reflect a stable individual trait difference in brain activity (e.g., Cox et al., 2018). Of note, there is a considerable lack of longitudinal evidence for long-term changes in CFC across time, with most studies following a cross-

sectional design. However, one study in children and adolescence showed that CFC increases during development across a 7-year follow-up period (Hahn et al., 2020).

Both spindle and ripple activity have been shown to increase during the SO down-to-up-state transition and during the up-state (Bandarabadi et al., 2019; Clemens et al., 2007; Cox et al., 2020; Dickey et al., 2021; Gonzalez et al., 2018; Mak-McCully et al., 2017; Mölle et al., 2006; Oyanedel et al., 2020; but see also Helfrich et al., 2019). Further, coupling with ripple activity is weakened or absent in the presence of damage to mesiotemporal brain structures (Clemens et al., 2007). There are also several reports that ripples (e.g., 100–200 Hz) are coupled to sleep spindles, and particularly during the excitable troughs of each spindle cycle (Clemens et al., 2011; Helfrich et al., 2019; Latchoumane et al., 2017; Ngo et al., 2020; Siapas & Wilson, 1998; Staresina et al., 2015). Sullivan and colleagues (2015) demonstrated that, during spindle events, HC ripples (> 90 Hz) were ~1.8 times greater compared to baseline time periods. Coupling between spindles and faster frequency oscillations may be further modulated by up and down phases of the neocortical SO (Jiang et al., 2019a), as demonstrated in frontal brain regions (Cox, van Driel, et al., 2014; Staresina et al., 2015) and in the retrosplenial cortex (Opalka et al., 2020). Helfrich et al. (2019) suggested that SOs trigger TC spindles, that spindle activity coupled with the SO up-state is predictive of connectivity patterns between pre-frontal cortex (PFC) and MTL spindles, and that both SOs and spindles could trigger HC ripple-based reactivations. Together, this system could promote HC-neocortical transactions and facilitate sleep-associated memory consolidation through a bidirectional communication process mediated by neocortical-HC-neocortical loops.

SO-Spindle-Ripple CFC and Memory. Experimental research in animals and humans offers compelling evidence that CFC plays a mechanistic role in learning and sleep-associated memory consolidation (Helfrich et al., 2019; Staresina et al., 2015; Ngo et al., 2020). For instance, Helfrich et al. (2019) showed that spindles coupled with the SO up-state predicted the connectivity of spindles between the PFC and MTL. Several human studies have demonstrated an association between SO – σ CFC and performance on tests of declarative (Cairney et al., 2018; Ladenbauer et al., 2017; Mikutta et al., 2019; Niknazar et al., 2015; Ruch et al., 2012; Zhang et al., 2020) and/or procedural learning (Bartsch et al.,

2019; Mikutta et al., 2019; Mylonas et al., 2020; Yordanova et al., 2017), although others have not (e.g., Cox et al., 2018; Demanuele et al., 2017), but it also depends on which measure was used. Interestingly, there may be laterality effects of coupling after a learning task based on which hemisphere was trained (Mylonas et al., 2020; Yordanova et al., 2017). Most studies of CFC and memory focus on fast spindle coupling (e.g., > 12 Hz) and include samples of healthy young or middle-aged adults (e.g., Bar et al., 2020; Bastian et al., 2022; Cairney et al., 2018; Dehnavi et al., 2021; Denis et al., 2021; Mikutta et al., 2019; Mölle et al., 2004, 2009, 2011; Mylonas et al., 2020; Niknazar et al., 2015; Perrault et al., 2019; Ruch et al., 2012; Yordanova et al., 2017; Zhang et al., 2020).

A handful of studies demonstrate that specific interventions during NREM sleep can optimize SO – σ timing (i.e., enhanced spindle/sigma power with the SO up-state) and improve memory. Methods to alter brain activity and CFC during sleep include the use of auditory stimulation (Krugliakova et al., 2020), TMR with olfactory (Bar et al., 2020; Bartsch et al., 2019) or auditory cueing (Schneider et al., 2020), examining the effects of certain drugs (Mylonas et al., 2020; Niknazar et al., 2015; Zhang et al., 2020), or applying transcranial direct current stimulation (tDCS) (Ladenbauer et al., 2017). There may also be specific effects or outcomes of cueing related to the natural and spontaneous co-occurrence of SO and spindle oscillations (e.g., Cairney et al., 2018, Schreiner et al., 2021). Overall, different measures of SO – σ coupling phase and coupling strength have been associated with performance on a variety of (declarative and procedural) memory tasks, albeit with distinct patterns of association in different populations and depending on certain analytic contexts, as will be made clear in subsequent paragraphs.

Coupling with faster (HC) oscillations has also been associated with memory performance, often interpreted in the context of memory reactivations during sleep. For instance, two studies both demonstrated that fast neural activity and population firing patterns observed during a pre-sleep wake period were “replayed” during subsequent sleep, and the fast (e.g., ripple) activity during sleep was coupled with NREM SOs and spindles (Dickey et al., 2021; Jiang et al., 2017). Mölle and colleagues (2009) also reported that odor-reward learning was associated with greater spindle-ripple synchrony in rats, but no association was found with the SO; conversely this same study noted in humans that pre-sleep

word-pair learning enhanced the correlation between SO (~2 Hz) time-locked increases in HC ripple activity (150–250 Hz) and in spindle activity (12–15 Hz). Current thinking is that spindles facilitate a temporally fine-tuned transfer of memory-related information from HC to neocortex, allowing fast-frequency activity to be expressed in the cortex at a time when long-term potentiation is more likely (e.g., spindle-triggered Ca^{2+} influx into pyramidal cells during up-states; Clemens et al., 2011; Ngo et al., 2020; Rosanova & Ulrich, 2005). However, spindle-ripple effects on memory may not necessarily depend on the SO phase (Valencia et al., 2013), and there may be functional differences between frontal versus centro-parietal spindle-ripple CFC (c.f., Clemens et al., 2011 and Latchoumane et al., 2017).

Taken together, growing evidence has implicated NREM sleep oscillations in overnight memory consolidation processes, both when examined in isolation or in combination, and when measured across cortical and sub-cortical brain regions. There is mounting evidence and a general consensus so far that phase-amplitude CFC during NREM sleep between cortical SO, TC spindle, and HC ripple activity is a candidate mechanism of overnight memory consolidation/stabilization (e.g., Latchoumane et al., 2017; Mölle et al., 2009; Ngo et al., 2020), in-line with the "active systems" consolidation hypothesis (Ackermann & Rasch, 2014; Cairney et al., 2015; Klinzing et al., 2019).

The Present Research: SO – σ CFC and Declarative Memory Consolidation in Healthy Ageing

The sections above provided a thorough, yet still not exhaustive, review of current knowledge about sleep oscillations and associations with learning/memory, cross-frequency coupling, and evidence for NREM coupling as a neural mechanism of sleep-associated memory consolidation. As well, the discussion above was mostly focused on results from studies with healthy young adults. Co-occurring declines with age in both sleep (quality, quantity) and memory performance has sparked considerable research interest into understanding how one relates to the other. Importantly, this effort has motivated investigations into relations between poor sleep and greater risk for ageing-related neurodegenerative disorders, such as mild cognitive impairment (MCI) and Alzheimer's disease (AD; e.g., Holth et al., 2017; Insel et al., 2021; Wang & Holtzman, 2020). A growing theory suggests that age-related declines in CFC may be implicated in the pathophysiology of age-related cognitive decline, and perhaps also

dementia, such as AD (Goutagny et al., 2013; Hamm et al., 2015; Lloret et al., 2020). However, as outlined below, there is a paucity of studies available examining relations between oscillation coupling during sleep and ageing-related cognitive impairments, and even fewer which study clinical groups with cognitive impairments and AD. The following section reviews changes in sleep observed in healthy older adults and, after this, in seniors with aMCI and AD. This is followed by a review of research examining ageing-related changes in NREM oscillations and their association with memory in healthy and cognitively impaired older adults. Finally, discussion will focus in on the available knowledge about SO – σ CFC in the context of ageing, to highlight the knowledge gaps that motivated this dissertation.

Changes in Sleep with Lifespan Ageing

Sleep disturbances are a common complaint among older adults (e.g., Reid et al., 2006). Epidemiological studies suggest that 10% of adults and 25% of older adults will experience chronic insomnia (i.e., >3 months; Lichstein et al., 2004; Morin et al., 2006). Sleep disturbances often manifest as poor sleep maintenance (e.g., frequent arousals from sleep), altered sleep-wake rhythms, and reduced time spent in SWS (Munch et al., 2004; Ohayon et al., 2004). Ageing also coincides with noted alterations in circadian rhythmicity: Older adults typically go to bed earlier and awake from sleep earlier than younger adults, and often nap more during the day (Buysse et al., 2005; Ohayon & Vecchierini, 2005). Older adults, especially older males, also show more frequent and prolonged awakenings across the night versus younger adults (Webb, 1982), which can be explained in part by a greater incidence of sleep disorders in the elderly, particularly sleep apnea and restless legs syndrome (Morrell et al., 2012; Stanley, 2005). Chronically poor sleep among older adults can also lead to increased stress and negative effects on one's emotional and mental health (e.g., frustration, irritability, hopelessness; Carey et al., 2004; Karlson et al., 2013; Lin et al., 2022).

Age-related changes in sleep (e.g., proportions of NREM and REM sleep, stability of sleep) likely reflect lifespan modifications in circadian and homeostatic regulation, neurophysiology and anatomy (e.g., grey matter volume), and TC network integrity, along with other changes in response to daily life stress (Steiger, 2007). Older adults spend more time in N1, less time in N3 and REM sleep, and have

more arousals across sleep stages versus teenage or middle-aged participants (Boselli et al., 1998; Moraes et al., 2014; Munch et al., 2004). Declines in sleep efficiency, sleep stability, and time spent in N3 and REM sleep continue across the 50th to 80th decade (Djonlagic et al., 2021). Indeed, a meta-analysis of 65 sleep studies from childhood to old age demonstrated that total sleep time decreases linearly by ~10 minutes per decade (Ohavon et al., 2004). A subsequent meta-analytic study of over 300 research reports suggested that the percentage of REM sleep declines linearly with increasing age, showing a decrease of ~0.6% per decade until the mid-70s (Floyd et al., 2007).

Ageing coincides with alterations or declines in neural oscillatory activity during sleep, and declines are evident even in the middle years of life. Middle-aged adults (average age of around 50 years old) evidence reduced slow wave density and amplitude, and longer hyperpolarization and depolarization phases (Carrier et al., 2011), as well as decreased power density in the SO/delta/theta (1.25–6 Hz) range during NREM sleep versus younger adults (Dijk et al., 1989). Older adults also display a blunted increase in delta EEG power (1.25–3.75 Hz) following 40-hours of sleep deprivation versus young adults (Munch et al., 2004). Compared to young adults, older adults also evidence decreased spindle density, amplitude, and duration; blunted slope of spindle activity across the night; and, decreased amplitude and density of K-complexes (Crowley et al., 2002; Gaudreau et al., 2001; Ladenbauer et al., 2021; see also Edwards et al., 2010 and Fogel et al., 2012 for reviews). A recent epidemiological study (Djonlagic et al., 2021), with participants ranging from 54 to 96 years old, demonstrated that greater age was associated with declines in SO count, density, slope, and amplitude, and increased SO duration (i.e., slower SOs), as well as reduced intra-spindle slowing and changes in spindle frequency (i.e., greater age was associated with slower slow spindles and faster fast spindles; see also Muehlroth & Werkle-Bergner, 2020, Figure 4). This large study also reported that older females (vs. males) had higher SO count, slope, and amplitude, higher spindle activity, and higher spectral power activity across the SO to beta frequencies (Djonlagic et al., 2021). Together, natural ageing is accompanied by alterations in sleep-wake rhythms, aberrant sleep architecture, and disrupted sleep oscillations.

Ageing can also negatively impact the normal functioning of the glymphatic system, which works to clear the brain of metabolic waste products that accumulate during wakefulness, and is primarily active during SWS (Hablitz & Nedergaard, 2021). Declines in glymphatic functioning in older adults is most likely related to the decrease in both SWS and SWA (see Hauglund et al., 2019 and Nedergaard & Goldman, 2020 for reviews). Disruption to the normal clearance of waste during sleep can cause, among other effects, an accumulation of β-amyloid deposits that can itself further impair both sleep quality and glymphatic functioning (also reviewed in Hauglund et al., 2019 and Nedergaard & Goldman, 2020). Naturally, this outcome has important implications for better understanding the intersections of ageing, sleep, and neural oscillations in the development of cognitive decline and neurodegeneration. The role of disrupted glymphatic functioning in older adults, and resulting downstream effects on synaptic activity, is also pertinent in understanding ageing effects on sleep-associated memory consolidation, and it adds context to the relevance of declines in SWS with ageing through the lens of both the SHY and active systems models of memory consolidation.

Changes in Sleep with Pathological Ageing

The changes observed in sleep and in sleep-wake rhythms among older adults become magnified and accelerated in the face of a pathology, such as dementia. Dementia is a broad category of several neurodegenerative disorder subtypes, each involving distinct neuropathologies, symptom constellations, and functional impairments. AD is a progressive neurodegenerative disease, and the most common type of dementia, broadly characterized by neuroanatomical atrophy, cognitive impairment, and reduced daily independence. Impaired short-term retention of knowledge and recent events are common early signs; with increased disease progression, worsening impairment is seen in long-term and episodic memory, executive functioning, language, visual orientation, and motivation and self-care (Porter et al., 2015; Stern et al., 1994). β-amyloid plaques and tau protein tangles represent hallmark neuropathological markers of AD, and both are associated with disruptions to normal neural functioning (Goutagny et al., 2013; Hamm et al., 2015; Lucey & Baterman, 2014), although tau deposits are often more strongly correlated with cognitive impairments/decline (Nedergaard & Goldman, 2020; Van Egroo et al., 2019).

There is a growing evidence base to support conclusions of a dynamic association between sleep and neurodegeneration, in the context of healthy ageing (Winer et al., 2019) and AD or MCI (Morris et al., 2001; Porter et al., 2015). Brain imaging studies indicate that sleep increases the rate of β-amyloid protein clearance from the brain (Xie et al., 2013), and that sleep deprivation impairs this normal decline in β-amyloid levels (Ooms et al., 2014); this finding has been supported by cross-sectional studies of self-reported sleep (Insel et al., 2021; Spira et al., 2013; Winer et al., 2019) and wrist actigraphy (Ju et al., 2013), and in longitudinal studies with wrist actigraphy (N = 698, M age = 81.7 years; Lim et al., 2013). Epidemiological research estimates that sleep disturbances, like chronic insomnia, is reported by around 35% of older adults experiencing cognitive decline (Mayer et al., 2011; Shub et al., 2009). More insomnia difficulties are associated with higher risk of developing cognitive symptoms and AD pathology in both cross-sectional (Benedict et al., 2015; see also Leng et al., 2020) and longitudinal studies (Lim et al., 2013; see also Lucey et al., 2021). A recent meta-analysis of 24 studies demonstrated significant reductions in sleep time, sleep efficiency, SWS and REM sleep, and increased sleep latency and number of arousals in AD versus controls; as well, the declines in SWS and REM sleep correlated with the degree of cognitive impairment (Zhang et al., 2022; see also Lucey & Bateman, 2014 for review).

Altered sleep oscillation activity with age may be especially pronounced in the context of aMCI and AD, potentially reflecting underlying pathophysiological process of dementia. One study showed reduced delta and theta power in aMCI versus controls (Westerberg et al., 2012), while another study found a faster mean theta power in AD patients (Hot et al., 2011). Ladenbauer and colleagues (2021) reported that MCI patients had lower SO power and amplitude versus young adults, but there were few or no differences with a healthy older adult group. There may also be stark declines in spindle activity (e.g., density, amplitude), and more-so with fast spindle activity, among cognitively impaired versus younger or older control groups (Gorgoni et al., 2016; Ladenbauer et al., 2021; Rauchs et al., 2008; Weng et al., 2020). Thus, evidence exists for group-level differences in sleep oscillations within cognitively impaired groups versus controls, and especially with reduced SO and spindle activity. Critically, a study with healthy seniors by Winer and colleagues (2019) reported a double-dissociation effect, such that SO – σ

CFC negatively predicted the severity of PET-measured tau burden in the MTL, but did not predict cortical amyloid burden, whereas the opposite was found with measures of SWA (i.e., predicting amyloid but not tau burden). The authors suggested that early taupathy in the MTL can interfere with normal SO-spindle-ripple dynamics and coupling, which may be relevant for memory consolidation; however, this was not directly tested as the study did not include a memory test.

Sleep Oscillations and Memory in Normal and Pathological Ageing

Cross-sectional research suggests that disturbed or altered sleep (e.g., insomnia) is associated with subjective cognitive complaints (e.g., poor concentration); moderate objective deficits in working memory, episodic memory, and executive function (e.g., problem solving); and anatomical differences in brain areas that are critical for cognitive processing (e.g., HC, PFC) versus healthy controls (e.g., Cross et al., 2019; O'Byrne et al., 2014; Shekleton et al., 2010 and 2014; Yao et al., 2021; see also Fortier-Brochu et al., 2012 for a meta-analysis). As well, prospective longitudinal studies in older adults suggest that worsening self-reported insomnia symptoms (e.g., trouble falling asleep, waking up too early, short sleep duration, daytime sleepiness) independently predicts cognitive decline (Cricco et al., 2001; Keage et al., 2012) and is related to more severe reports of subjective memory decline (Zhao et al., 2022).

Given the changes in sleep, cognition, and neuroanatomy that coincide with greater age, there may be pertinent relations between brain oscillations, and CFC, during sleep in older adults that help explain the observed memory deficits. A meta-analysis of 22 studies examining sleep-associated memory performance between young and older adults found an overall beneficial effect of sleep in younger but not older adults, and with specific effects related more to sleep-associated declarative, but not procedural, memory consolidation (Gui et al., 2017). It is possible that age-associated declines in SWS acts as a fundamental context in which disruptions to normal sleep-associated memory processes can occur (e.g., Backhaus et al., 2007). In turn, more shallow and less stable sleep (i.e., more arousals) among older adults limits opportunity to generate SO-rich sleep, which weakens the "protective bubble" that is formed by sleep against external/interfering stimuli, and interrupts normal HC-neocortical dynamics required for sleep-associated memory consolidation.

Among cognitively normal seniors, reduced prefrontal fast spindle activity mediated the relation between older age and reduced episodic recall performance (Mander et al., 2013), while reduced SWA mediated the association between medial PFC β-amyloid deposition and impaired HC-dependent memory consolidation (Mander et al., 2014 and 2015). Declarative memory performance in older adults has been associated with greater SWA (Papalambros et al., 2017) and higher spindle density (Lafortune et al., 2014) during NREM sleep. Djonlagic and colleagues (2021) also found in older adults that a higher spindle count and higher sigma power during N2, and decreased SO duration (i.e., faster SOs) was associated with better cognitive performance (e.g., executive functioning, processing speed), whereas higher relative SO power and lower relative delta (1–4 Hz) power correlated with worse performance. Among cognitively impaired patients (vs. controls), reduced spindle activity was associated with worse immediate word and story recall (Rauchs et al., 2008), and with scores on the mini mental state exam (Gorgoni et al., 2016). Patients with aMCI and AD have also shown faster theta (4–7 Hz) activity during SWS versus controls, associated with better recall on sleep-associated memory tasks (Westerberg et al., 2012), potentially reflecting an early signal of dementia and compensatory mechanism (Hot et al., 2011). Together, while more research is clearly needed in clinical populations, results of various studies suggest that age-related declines in sleep and alterations in cardinal (delta, spindle, theta) sleep oscillations can at least partially account for cognitive and memory declines that accompany normal (and perhaps also pathological) ageing (Edwards et al., 2010; Fogel et al., 2012).

SO – σ Coupling and Lifespan Ageing

To our knowledge there is only a small handful of studies available to examine SO – σ CFC in older adult samples (Djonlagic et al., 2021; Helfrich et al., 2018; Ladenbauer et al., 2017; Ladenbauer et al., 2021; Muehlroth et al., 2019; Sattari et al., 2019; Schneider et al., 2020; Sunwoo et al., 2021; Winer et al., 2019; see also McConnell et al., 2022). Collectively, these studies suggest that (fast) spindle activity peaks earlier in the SO rising phase in older adults, and that this mistiming in aged samples is associated with worse memory. Slow spindle coupling is also mistimed, peaking earlier in the SO up-to-down-state transition phase (i.e., after the up-state) among older relative to younger adults (Ladenbauer et al., 2021;

Muehlroth et al., 2019). More recently, a large study with just older adults Djonlagic et al. (2021) reported marked reductions with greater age in coupling strength for both fast and slow spindle metrics, and in the occurrence of SO-spindle complexes (especially in males). Thus, there is growing evidence for a natural SO-spindle "de-coupling" with greater age; however, due to the limited number of studies comparing younger and older adults, especially in the context of memory, there are important gaps in knowledge regarding how ageing impacts SO – σ CFC, what factors contribute to the rate and magnitude of age-related changes/declines, and the functional consequences of this "de-coupling".

It is possible that age-related declines in normal coupling dynamics are more pronounced in the context of neurodegeneration. While there is some evidence for decreased coupled brain activity during awake periods being associated with AD pathology in rats (Goutagny et al., 2013) and AD disease severity in humans (Fraga et al., 2013), there is a paucity of studies examining group-level differences between seniors with cognitive impairment versus healthy controls in the context of SO – σ CFC during sleep. A recent nap study (Ladenbauer et al., 2021) is among the first to directly compare SO – σ CFC between healthy young adults, and older adults without and with MCI. Chiefly, precise SO – σ coupling was more strongly attenuated in MCI compared to healthy controls (e.g., deteriorated fast spindle activity during the down-to-up-state transition, less inhibited spindle activity after the up-state), but there were no differences between groups in measures of coupling strength.

Together, there is emerging evidence for age-related declines in SO – σ CFC in healthy older versus younger adults. There may be similar declines in SO – σ coupling between healthy and cognitively impaired seniors, however direct empirical evidence for this is generally lacking at present. More studies are clearly needed to better understand differences in coupling patterns between healthy and pathological ageing, and how these patterns relate to overnight memory consolidation.

SO – σ Coupling and Memory in Older Adults

It has been hypothesized that ageing-related declines in SO – σ CFC could explain the accompanying declines in memory consolidation during sleep in older adults. However, to our knowledge, only a portion of available studies with seniors directly compare SO – σ CFC between

younger and older adults in the context of sleep-associated memory consolidation (Helfrich et al., 2018; Ladenbauer et al., 2021; Muehlroth et al., 2019; Schneider et al., 2020). Overall, there is a general consensus from available studies that the mistiming of (fast) spindle activity with the SO peak in older versus younger adults is associated with impaired memory consolidation. Muehlroth and colleagues described that a "youth-like" SO-fast spindle coupling pattern, with a peak at or just after the up-state, is associated with better memory retention; the older adults with a "youth-like" coupling pattern did better on memory testing, whereas older (and younger) adults with a more "aged" pattern (fast spindle activity peaking too early before the up-state, stronger slow spindle power increases between the up-state and down-state) showed worse memory. However, a recent older adult cohort study (Djonlagic et al., 2021) demonstrated that stronger coupling strength (e.g., vector length) was associated with better performance on neuropsychological tests, and this was true for both fast and slow spindle coupling. Important in the context of memory, there may be a linear relationship between the precision of SO-spindle timing and grey matter volume in the medial PFC (Helfrich et al., 2018) and the thalamus (Muehlroth et al., 2019).

There are limited studies available which examine SO – σ CFC in seniors with cognitive decline versus controls. In a nap study of 12 seniors with MCI, Ladenbauer et al. (2017) showed that electrical stimulation during sleep improved SO-spindle coupling precision and recognition memory performance, but this study did not have a healthy control group. A subsequent nap study with data from healthy young adults, healthy older adults, and seniors with MCI (Ladenbauer et al., 2021) demonstrated significant group differences in performance on a word-pair task but not on a picture recognition or location memory task; however, this study did not observe significant associations between major sleep parameters and memory across groups, or for associations between coupling and pre- to post-sleep performance change.

Summary and Overview of the Current Research

To summarize, sleep is characterized by reliable changes in oscillatory brain activity that reflect different stages of sleep depth. A growing interest in brain oscillation activity during sleep and SO – σ CFC has yielded empirical data allowing for new insights into underlying mechanisms of sleep-associated memory consolidation, in-line with the "active systems" model, with most evidence available from

studies with healthy young adults. Ageing coincides with disruptions in sleep quantity and quality, and by alterations in neural oscillatory activity during sleep, both of which are related to cognitive impairments such as those seen in aMCI and AD. Mounting evidence suggests that disrupted SO – σ CFC (such as in ageing) is associated with impaired overnight memory consolidation, and that CFC may be suited as a non-invasive biomarker of cognitive decline and AD. However, there is a paucity of studies available to directly compare SO – σ CFC between younger and (healthy or impaired) older adult groups, and especially in the context of memory consolidation. Of the studies that do exist, there are noted differences in their methodology (e.g., memory paradigm) and analysis (e.g., sleep stage of interest, type of coupled activity) make it challenging to draw firm conclusions. This, in turn, makes for an important gap in knowledge, and one that needs to be filled before stronger inferences can be made about CFC during sleep in relation to ageing and overnight memory consolidation.

The overarching aim of this dissertation is to examine associations between SO – σ CFC during sleep and overnight memory consolidation in the context of healthy lifespan ageing. To address the knowledge gaps outlined above, my thesis includes two related studies that both examine SO – σ CFC and relations with declarative memory consolidation. The first study examines CFC during NREM sleep in a sample of just older adults, and the second study examines the same measures in a new sample of older adults who were compared with a young adult control group. It is hoped that these two studies can help offer new or expanded insights into the functions of coupled oscillations during NREM sleep, and potential neural mechanisms of sleep-associated memory consolidation in relation to healthy ageing.

Research Objectives and Hypotheses

There are two primary aims of my research. The first aim is to provide novel data related to coupled brain activity in healthy older adults, and the second aim is to add to a currently limited knowledgebase regarding associations between SO – σ CFC and memory consolidation across the adult lifespan. To this end, two studies were conducted, both examining sleep data from healthy older adults. In Study 1, I first provide a comprehensive examination of CFC and memory in a sample of 25 healthy older adults who completed a 2-night study protocol, with an emphasis on coupling with slow spindle activity

and relative change in coupling between a learning task night and a non-learning baseline. Next, in Study 2, my first examination is replicated in a new sample of healthy older adults who completed an expanded 3-night study protocol that included both a young adult control group and a non-learning cognitive control task, both of which helped to enhance the methodological control of this study.

There are three overarching hypotheses that are tested in this research, which stem from insights gained during my literature review. First, I hypothesized that measures of SO – σ CFC during NREM sleep will be enhanced (e.g., stronger, more precisely timed with the up-state) after a pre-sleep declarative learning task, compared to a non-learning condition. Second, I hypothesized that greater coupled brain activity will be associated with better performance on the memory task; more specifically, I will examine if differences in the individual-level change (increase or decrease) in CFC between experimental conditions can predict memory. Third, I hypothesized seeing age-group-level differences in measures of coupling strength and coupling phase when older participants are directly compared to younger adults.

Both included studies examine the same coupling measures, with an emphasis on slow spindle CFC derived using a fixed bandwidth, and both studies examine relations with performance on a 40-item word-pair associates task. An additional aim of my second study is to examine the impact on my results when I account for individual differences in brain activity; this is done by examining complementary data sets of CFC derived using a fixed spindle bandwidth compared to individually adapted bands based on spectral peaks. My final thesis chapter aims to synthesize the observations and impressions gleaned across my two studies and integrate them with available related studies. I will also expand on discussion points that I raise throughout regarding methodology in this line of research. Lastly, I propose specific pathways to help broaden the current conceptual framework regarding the intersection of CFC, memory, and ageing, and discuss practical and clinical implications of this work.

Slow Oscillation-Spindle Cross-Frequency Coupling Predicts Overnight Declarative Memory Consolidation in Older Adults

Oren M. Weiner[1,2], Jordan O'Byrne[1,3], Nathan E. Cross[1,2], Julia Giraud[4], Lukia Tarelli[1,2], Victoria Yue[1], Léa Homer[1], Katherine Walker[1], Roxanne Carbone[1], and Thien Thanh Dang-Vu[1,2,4]

[1]PERFORM Centre and Center for Studies in Behavioural Neurobiology, Department of Psychology and Department of Health, Kinesiology, and Applied Physiology, Concordia University, Montréal, Quebec, Canada

[2]Centre de Recherche de l'Institut Universitaire de Gériatrie de Montréal, CIUSSS Centre-Sud-de-l'île-de-Montréal, Montréal, Quebec, Canada

[3]Department of Psychology, Université de Montréal, Montréal, Quebec, Canada

[4]Department of Neurosciences, Université de Montréal, Montréal, Quebec, Canada

Keywords: Sleep, Brain Oscillations, Cross-Frequency Coupling, Overnight Memory Consolidation, Ageing

Manuscript Published in the *European Journal of Neuroscience*

doi: http://doi.org/10.1111/ejn.15980

Abstract

Cross-frequency coupling (CFC) between brain oscillations during non-rapid-eye-movement (NREM) sleep (e.g., slow oscillations (SO), spindles) may be a neural mechanism of overnight memory consolidation. Declines in CFC across the lifespan might accompany coinciding memory problems with ageing. However, there are few reports of CFC changes during sleep after learning in older adults, controlling for baseline effects. Our objective was to examine NREM CFC in healthy older adults, with an emphasis on spindle activity and SOs from frontal EEG, during a learning night after a declarative learning task, as compared to a baseline night without learning. Twenty-five older adults (*M* (SD) age = 69.12 (5.53) years; 64% female) completed a 2-night study, with a pre- and post-sleep word-pair associates task completed on the second night. SO-spindle coupling strength and a measure of coupling phase distance from the SO up-state were both examined for between-night differences and associations with memory consolidation. Coupling strength and phase distance from the up-state peak were both stable between nights. Change in coupling strength between nights was not associated with memory consolidation, but a shift in coupling phase *towards* (vs. away from) the up-state peak after learning predicted better memory consolidation. As well, an exploratory interaction model suggested that associations between coupling phase closer to the up-state peak and memory consolidation may be moderated by higher (vs. lower) coupling strength. This study supports a role for NREM CFC in sleep-related memory consolidation in older adults.

Slow Oscillation-Spindle Cross-Frequency Coupling Predicts Overnight Declarative Memory Consolidation in Older Adults

An extensive body of work has linked memory consolidation with brain oscillations that occur during non-rapid-eye-movement (NREM) sleep. The synchronization, or cross-frequency coupling (CFC), of brain oscillations has been given recent attention as a potential neural mechanism of sleep-associated, or "offline", memory consolidation. In the context of NREM sleep, a primary focus has been on studying phase-amplitude CFC between the cortical slow oscillation (SO) and thalamo-cortical (TC) sleep spindle activity. The SO occurs when large assemblies of cortical neurons synchronize between a depolarized up-state and a hyperpolarized down-state (Steriade, Contreras et al., 1993; Steriade, Nunez, & Amzica, 1993a). The SO (typically < 1 Hz; > 70 μV) is generated in the neocortex (Timofeev & Steriade, 1996; Steriade, Nunez, & Amzica, 1993b), but may be modulated by thalamic and TC inputs (c.f., Amzica & Steriade, 1995; Blethyn et al., 2006; Steriade, Contreras et al., 1993, Steriade et al., 1993b). Sleep spindles are oscillations at a sigma frequency range (typically 11–15 or 16 Hz), which last 0.5 to 3 sec (Iber et al., 2007), and are attributed to interactions between thalamic reticular, TC, and cortical pyramidal networks (Dang-Vu et al., 2011; Fernandez & Lüthi, 2020; Steriade, McCormick, & Sejnowski, 1993; Timofeev & Steriade, 1996). Sleep spindles, and proxy-measures of sigma (σ) power, have been shown to promote sleep stability (Dang-Vu et al., 2010; see also Fernandez & Lüthi, 2020) and memory (Clemens et al., 2005; Cox et al., 2012; Mölle et al., 2011; see also Kumral et al., 2022 for a recent meta-analysis of spindles and memory). As well, there is evidence that spindle activity is stable within subjects across time (a "spindle fingerprint"; De Gennaro et al., 2005; Fernandez & Lüthi, 2020).

Phase-amplitude CFC reflects the association or synchronization between the phase of a slower oscillation and amplitude of a faster oscillation, and is typically quantified using measures of coupling strength and coupling phase. Measures of coupling strength (e.g., mean vector length, modulation index) reflect the extent of modulation in amplitude of a faster-frequency oscillation in relation to the up-and-down phase of a slower-frequency oscillation (c.f., Hülsemann et al., 2019). Measures of coupling phase

reflect the average point in time (i.e., mean phase-angle direction in circular space from 0-360°) on the slower oscillation where the faster oscillation amplitude is highest.

Several studies have demonstrated that fast spindle activity (e.g., 12–16 Hz) in healthy adults tends to increase following the SO down-state, and reaches its maximum amplitude or power often during or surrounding the depolarizing SO up-state peak (e.g., Cox, van Driel et al., 2014; Helfrich et al., 2018; Mölle et al., 2002; Mölle et al., 2011; Niknazar et al., 2015). By contrast, slower spindles (e.g., 9–13 Hz) often reach a maximum peak during the SO up-to-down-state transition and towards the down-state peak (e.g., Mölle et al., 2011; Muehlroth et al., 2019; Yordanova et al., 2017). Slow-oscillation-to-sigma CFC (SO – σ CFC) is one part of a larger process of coordinated neural activity that occurs between cardinal NREM oscillations. Chiefly, as cortical SOs group TC spindles, the "trough" phase of spindle oscillations in turn group hippocampal (HC) ripple activity (Clemens et al., 2007; Staresina et al., 2015; Sullivan et al., 2015). This triple phase-locking of SO, spindle, and ripple activity is argued as a mechanism to support a HC-neocortical dialogue during NREM sleep, in line with the active systems consolidation model of sleep-dependent memory processes (e.g., Ackermann & Rasch, 2014; Cairney et al., 2015; Todorova & Zugaro, 2020).

The hypothesis that SO – σ CFC facilitates memory is supported by experimental work, however this specific area of research is still in early phases, as only a relative minority of studies to examine CFC during sleep did so in the context of memory. There are a number of studies to date which have demonstrated that overnight memory consolidation is positively associated with fast spindle (e.g., 12–15 Hz) activity coupled with the SO up-state peak (e.g., Bar et al., 2020; Ladenbauer et al., 2017; Mikutta et al., 2019; Muehlroth et al., 2019; Ngo et al., 2013; Niknazar et al., 2015; Schreiner et al., 2021). Conversely, fewer studies have examined relations between learning/memory and SO coupling with slow spindle activity: One study reported inconsistent increases in slow spindle activity after a word-pair learning task (Mölle et al., 2011), another reported that greater CFC with slow (vs. fast) spindle activity near the up-state in young adults is associated with worse scene-word memory (Muehlroth et al., 2019), and a third study reported that more slow spindle power in time with an SO (i.e., up-to-down-state

transition) was associated with lower response latency on a (spatial navigation) memory task (Bastian et al., 2022).

Most available studies of CFC and memory include samples of healthy young adults (e.g., Bar et al., 2020; Bastian et al., 2022; Cairney et al., 2018; Dehnavi et al., 2021; Denis et al., 2021; Mikutta et al., 2019; Mölle et al., 2004, 2009, 2011; Niknazar et al., 2015; Perrault et al., 2019; Ruch et al., 2012; Yordanova et al., 2017; Zhang et al., 2020). However, there is a general paucity of studies that examine CFC and memory among more middle-aged (Bartsch et al., 2019; Demanuele et al., 2017; Mylonas et al., 2020; Schneider et al., 2020) and older adult participants (Helfrich et al., 2018; Ladenbauer et al., 2017; Ladenbauer et al., 2021; Muehlroth et al., 2019). Both SOs and spindles are NREM oscillations whose activity (e.g., density, amplitude) declines with older age (e.g., Carrier et al., 2011; Martin et al., 2013), and there is some evidence that the same is true for SO – σ CFC. Schneider and colleagues (2020) demonstrated that memory-associated benefits of SO-timed auditory stimulation, and related coupling response, was weaker in middle-aged adults relative to a young adult dataset. Two recent studies (Helfrich et al., 2018; Muehlroth et al., 2019) both demonstrate that fast spindle activity peaks earlier in the SO rising phase in healthy older versus younger adults, and that SO – σ de-coupling in older age is associated with reduced grey matter volume in the medial PFC, as well as worse performance on tests of declarative memory. A fourth study in older adults with mild cognitive impairment (Ladenbauer et al., 2017) demonstrated that transcranial direct current stimulation applied during post-learning N2 sleep enhanced fast spindle coupling with the SO up-state versus a sham condition, and a stronger SO-spindle synchronization index in the stimulation condition was associated with better visual recognition memory.

Together, there is some early evidence for ageing-related changes in SO – σ CFC during sleep, and that weak or poor synchronization between SO and spindle activity in older adults may help explain memory impairments that coincide with ageing. However, relatively less is known about relations between SO – σ CFC and memory in the context of lifespan ageing. As well, of the available studies of SO – σ CFC and learning/memory, many of them rely on or showcase data from only one sleep recording visit (e.g., Bar et al., 2020; Cairney et al., 2018; Cross et al., 2020; Helfrich et al., 2018; Mikutta et al.,

2019; Muehlroth et al., 2019). Such absence of a baseline control night limits inferences about whether SO – σ CFC is more of a state-dependent oscillatory phenomenon that can be manipulated by pre-sleep experience, or a stable, trait-like activity that reflects general cognitive abilities.

Given the current state of knowledge about SO – σ CFC and memory above, the current study had two specific major aims: First, we examined whether learning a declarative memory task changes SO – σ CFC during subsequent sleep in healthy older adults. For this we hypothesized that SO – σ coupling strength would be increased, and the corresponding coupling phase would be closer to the SO up-state, during sleep after a declarative learning task versus a baseline night with no task. Second, we examined whether SO – σ CFC during sleep between nights (i.e., after learning vs. before) is related to performance on the sleep-dependent declarative memory task. For this we hypothesized that stronger coupling strength and coupling phase closer to the SO up-state after completing the learning task will be associated with better overnight memory consolidation. Following these two major aims, we also conducted an exploratory examination to see if a more complex dynamic in predicting memory consolidation is revealed when we consider a statistical interaction between the two measures of coupling strength and coupling phase measured after a pre-sleep learning period (e.g., if one moderates the other).

Materials and Methods

Participants and Recruitment Procedure

Healthy older adults were recruited from the general Montréal community. Participants were recruited using a two-stage evaluation, involving (1) a brief, telephone-based screening interview, and (2) an in-person assessment of sleep and general health, and to screen cognitive functioning. The in-person interview assessed sleep (e.g., regularity, quality), health (e.g., medication, medical history), physical activity (e.g., weekly exercise), and daily habits (e.g., caffeine use, alcohol). Participants also completed the Mini Mental State Exam (MMSE; Crum et al., 1993; Magni et al., 1996; Tombaugh & McIntyre, 1992) and Montreal Cognitive Assessment (MoCA; Nasreddine et al., 2005; Rossetti et al., 2011), and a battery of questionnaires.

Older adults (55–85 years-old) were eligible for this study if they satisfied the following *a priori* criteria: no chronic/unstable medical condition (e.g., infection, acute and severe medical event, uncontrolled diabetes); not having a sleep disorder (e.g., chronic insomnia [sleep difficulty > 3 nights per week for > 3 months], severe sleep apnea [defined by AHI ≥ 30/hr], parasomnia); no excessive alcohol use (i.e., drinks ≤ 10 glasses/week) or use of illicit drugs (including cannabis > 1 time per month); not currently working night shifts, and/or has not travelled through more than one time zone during the last six weeks; no history of brain hemorrhage, tumor, or any condition that required brain surgery; no major psychiatric (e.g., psychosis, mood disorder) or neurological disorders/acute neurological disease (< 1 yr; e.g., stroke, epilepsy); and, not currently using a hypnotic or any other psychotropic medication on a regular basis, and no medications that otherwise impact alertness or sleep. Older adults were excluded if they scored < 27 on the MMSE and/or < 24 on the MoCA. Volunteers were also excluded if they surpassed threshold scores on two or more screening questionnaires based on the following criteria: Insomnia Severity Index (≥ 15; Bastien et al., 2001; Morin et al., 2011); Pittsburgh Sleep Quality Index (≥ 5; Buysse et al., 1991); Epworth Sleepiness Scale (≥ 10; Johns, 1991, 1992); Stop-BANG sleep apnea screening questionnaire (≥ 5; Boynton et al., 2013; Silva et al., 2011); Horne-Östberg Morningness-Eveningness Questionnaire (≤ 30, "Very Evening" types; Horne & Östberg, 1976; Taillard et al., 2004); Geriatric Depression Scale (≥ 15; Yesavage et al., 1982); Geriatric Anxiety Inventory (≥ 10; Pachana et al., 2007).

A total of 43 older adults were deemed eligible after the interview and scheduled for their first recording night, used to rule out the presence of sleep disorders, primarily severe sleep apnea, and to act as a baseline. Participants with mild or moderate sleep apnea were retained to not impose overly strict criteria for older adults that could limit the generalizability of our study. Six of the original 43 participants were excluded after Night 1 due to severe sleep apnea or otherwise abnormal sleep, and a 7th participant withdrew. The remaining 36 eligible participants completed a second visit (learning/memory task night) at least one week later. Among these, 11 were later excluded (n = 1 for technical/recording problems, n = 6 for poor sleep efficiency [< 70%] on one or both nights, n = 4 for poor testing performance [pre-sleep

recall score < 10]). In our aim to examine learning and overnight memory consolidation in cognitively healthy older adults, we chose to exclude participants who evidenced especially poor initial encoding and retention of our word-pair stimuli, and thus had limited information available to consolidate during overnight sleep. The final sample was comprised of 25 participants.

Study Protocol

The study protocol is displayed in Figure 1. Participants were scheduled to arrive at the lab on both nights between 7pm and 9pm, adjusted for individual schedules. Both overnight sleep recordings included standard polysomnography (PSG) recordings (see below) that took place in a private bedroom in our sleep laboratory. Participants were instructed to abstain from drinking alcohol or excessive caffeine in the 24-hrs before each visit. Upon arriving for their Night 1 visit, participants were given instructions for completing a daily sleep diary, and for using aa wrist actigraphy device (Actiwatch) wristwatch to be worn daily until their second visit. Participants returned at least 7 days later to complete their Night 2 visit, which proceeded after verifying that their sleep patterns in the last week were stable/regular and typical for each person across the study interval between sleep recordings.

The second recording visit included a pre- and post-sleep word-pair associates memory task, completed after the equipment set-up (see below). Participants were tested on the word-pair task in either French or English, depending on which language they learned first and were most comfortable using in daily life. Immediately after the word-pair task learning period (described below), participants completed a pre-sleep recall task (PM recall) and were then free to go to bed according to their reported usual bedtimes. The next morning, participants were offered a light breakfast, and when ready, began the post-sleep cued-recall test (AM recall). AM recall testing began an average (*SD*) of 29.04 (13.39) minutes after Lights On. Following the AM test, participants completed two additional cognitive tasks: an N-back, and a Go/no-go task; data from these additional tasks are not reported here, as the primary focus of this study is on SO-sigma (SO – σ) CFC and relations with overnight declarative memory consolidation. After finishing all three morning tasks, participants were disconnected from the recording equipment and offered shower facilities and monetary compensation. All study procedures and documents were approved

by designated ethics committees at both Concordia University and the Centre de recherche de l'Institut universitaire de gériatrie de Montréal (CRIUGM), and all volunteers provided written consent before participating.

Hereafter, the first (Night 1) recording is referred to as the "baseline" visit, whereas the second (Night 2) recording is referred to as the "learning" visit.

Cognitive Testing: Word-Pair Associates Task

The primary task used in this study is a variant of the word-pair associates task (Backhaus et al., 2007; Plihal & Born, 1997). This task was chosen to maintain consistency with other related studies (e.g., Mölle et al., 2004, 2009, 2011; Zhang et al., 2020), and because it is designed as a task of HC-dependent associative memory. The task we designed included 40 pairs of nouns with minimal semantic similarity. Nouns were of standardized length (5–9 characters), word-frequency (> 5 per million; e.g., Corpus of Contemporary American English [for English words]; Lexique 3, http://www.lexique.org/ [for French words]), and emotionality (within a broadly neutral range; Bradley & Lang, 1999; Warriner et al 2013). Equivalent lists were developed in both English and French, balanced to match the words used in each list as closely as possible. Before starting the task, participants were shown instructions on-screen and given additional verbal explanation. Word-pairs were presented on a computer screen as vertically stacked and in large-text font. A blank screen followed each presentation, and a centered fixation cross indicated the next word-pair is coming up. During the blank screen, participants were instructed to form a visual mental image of the two words just presented, as a strategy to facilitate the forming of word associations. Word-pair stimuli were presented in 2 learning trials. During the first learning trial, stimulus presentation was 5-sec, followed by a 5-sec blank screen, and a 5-sec fixation cross to indicate that the next pair is coming up. During the second learning trial, stimulus presentation was 3-sec long, followed by a 3-sec blank screen, and 5-sec fixation cross. Word-pairs were arranged randomly between the first and second learning trials to reduce primacy and recency effects. Each learning trial was followed by a 2-minute break period. Including instructions and rest periods, duration of the learning trial was approximately 25 minutes.

After all word-pairs were presented twice, and after the second 2-minute break, participants underwent a short-delay cued-recall test (PM recall), where they were shown the first word in a pair on the screen and asked to recall the second word verbally. A research assistant scored verbal responses. Participants pressed a keyboard button after each response to proceed to the next trial, allowing for an unrestricted recall time. The post-sleep (AM recall) test consisted only of the cued-recall procedure and was identical to the pre-sleep test, except that word-pair cues were randomized again. No feedback was given to participants after responding on either test. The primary outcome variable was a measure of overnight memory consolidation, calculated as the number of correct word-pair responses involving the *same* word-pairs during both PM and AM recall tests. This approach is consistent with previous studies of sleep and memory examining the overnight "maintenance" of remembered items (e.g., Dumay, 2016; Muehlroth, Sander et al., 2020)

Overnight Sleep Recordings

The first overnight sleep recording consisted of a full PSG set-up, with electroencephalogram (EEG), electrooculogram (EOG), electromyogram (EMG), and electrocardiogram (ECG) sensors, a transcutaneous finger pulse oximeter (SpO2), and measures of respiration (oral-nasal thermocouple and nasal pressure cannula, thoracic and abdominal piezo-electric belts), and leg movements (leg EMG). The PSG electrode montage included 12 channels, positioned according to the American Academy of Sleep Medicine (AASM) International 10-20 placement system (Fz, F3, F4, Cz, C3, C4, O1, O2, M1, M2, Pz reference, Fpz Ground). The first (PSG) visit provided a baseline measure of brain activity during sleep. Respiratory and SpO2 monitoring alongside EEG during the first recording night allowed for screening and exclusion of older adults with severe sleep apnea.

Participants returned for the second EEG overnight visit at least seven days after the first visit (See Figure 1). EEG recordings consisted of an 18-channel montage (Fz, F3, F4, F7, F8, Cz, C3, C4, T3, T4, P3, P4, T5, T6, O1, O2, M1, M2, Pz online reference, Fpz Ground), plus measures of eye movements (EOG), chin muscle tone (EMG), and cardiac activity (ECG). All primary physiological signals were

collected using Domino equipment and software (bandpass filter 0.2–128 Hz, EEG sampling rate 512 Hz; SomnoMedics, Randersaker, Germany), on both nights.

EEG Analysis

Sleep records were scored for different sleep stages using Domino software, and subsequently processed using an open-source Python software package ("Wonambi"; https://github.com/wonambi-python/wonambi), developed in-house. Sleep EEG data was visually scored in 30-sec epochs in one of four stages of sleep (N1, N2, N3, REM) by an experienced sleep scorer according to standard criteria (e.g., Iber et al., 2007), and with consideration of smaller slow wave amplitude in older adults when scoring N2 and N3 (Webb & Dreblow, 1982). Sleep cycles were identified as periods of sleep containing at least 15 minutes of NREM sleep and 5 minutes of REM sleep, except for the first sleep cycle, which could contain > 0 minutes of REM (Feinberg & Floyd, 1979). An exception was made when there was no identifiable period of REM sleep occurring in the first sleep cycle; in this rare case, the cycle end was marked during a clear period of wakefulness or prominent arousal from sleep that occurred between around 90 to 120 minutes after stable sleep onset.

EEG sleep recordings for each participant on both study nights were reviewed in 30-sec epochs to identify artefacts or otherwise poor/interrupted signal and tag them for exclusion from later analysis. A secondary pass using 15-sec epochs was performed, if necessary, to reduce uncertainty when present. Signal aberrations targeted for removal included poor/dysfunctional signal > 1 sec (e.g., signal popping, flat-lining), excessive muscle artefact or movement, micro-arousal activity (e.g., sudden burst of sustained (> 3 sec) faster-frequency activity, usually associated with elevated chin EMG), or periods in an epoch that contained a shift to N1 or wakefulness.

Slow Oscillation and Spindle Detection

Automatic detection of slow oscillation (SO) and spindle events was performed using Wonambi, applying previously validated detection algorithms. SOs were detected using an algorithm described by Staresina and colleagues (2015). SOs were detected from separate N2 and N3 sleep stages using artefact-free EEG data filtered between 0.16–1.25 Hz (zero-phase infinite impulse response bandpass filter). Next,

candidate SO waves were identified based on zero-crossings in the filtered signals (down-states followed by up-states), as well as event duration and amplitude criteria. Event duration was defined as the time between two successive positive-to-negative zero-crossings, limited to within 0.8–2 sec. Event amplitude (trough-to-peak amplitude between two positive-to-negative zero crossings) was determined individually, based on amplitudes that exceeded the 75th percentile of candidate amplitudes for that participant. The resulting SO detection fell within a bandwidth of 0.5–1.25 Hz.

Spindle detection (based on Mölle et al., 2011) was performed using artefact-free EEG data in separate N2 and N3 sleep stages. Spindles were detected using a fixed bandwidth in the slow spindle range on Fz (9–13 Hz), and in the fast spindle range on Cz (12–16 Hz), given the frontal and central predominance of slow and fast spindles, respectively (Cox et al., 2017; Fernandez & Lüthi, 2020; Werth et al., 1997). After band-pass filtering artefact-free data within each frequency band, the root-mean-square (RMS) of the filtered signal was calculated at each data point using a 0.2 second sliding window, and subsequently smoothed with additional filtering. RMS values exceeding thresholds by 1.5 SD for between 0.5 and 3 seconds were identified as spindles.

Event-Locked Cross-Frequency Coupling

SO – σ phase-amplitude CFC during the total NREM (N2+N3) period was analyzed using SOs detected from N2 and N3 sleep stages, following concatenation. We combined the N2 and N3 detections to account for the occurrence of SOs in both sleep stages (e.g., Malerba et al., 2018; Menicucci et al., 2009). Coupling analyses performed on detected EEG events minimizes detection of spurious coupling in the data by ensuring a rise in power in the phase-giving frequency range (c.f., Aru et al., 2015). Specialized analysis scripts constructed phase-amplitude distributions on each detected SO event, and from this data we calculated the Modulation Index (MI; Tort et al., 2010) and measures of preferred coupling phase. Primary analyses focused on SO – σ CFC from frontal (Fz) EEG data across both study nights, given the frontal predominance of SO (Bersagliere et al., 2018; Massimini et al., 2004). The 9–13 Hz fixed frequency band we used is largely consistent with previous examinations of spindle frequency characteristics (e.g., Cox et al., 2017; Ujma et al., 2015) and studies of SO – σ CFC on frontal channels

(e.g., Klinzing et al., 2016; Ladenbauer et al., 2017; Muehlroth et al., 2019; Yordanova et al., 2017). Analyses on Cz data (12–16 Hz) are reported in the supplementary material.

The MI (Tort et al., 2010) is an information-theoretic metric based on the Kullback-Leibler distance function, which allows a model-free quantification of the divergence between two statistical distributions. Empirical distributions obtained from the phase-amplitude data are compared using a Shannon entropy approach with a template distribution that assumes no coupling effects, depicted by a flat/uniform distribution (Hülsemann et al., 2019). The MI ranges from 0–1, with larger values reflecting greater coupling strength between two oscillation frequencies. For each participant on each study night, SO – σ MI was calculated from detected SO events across the whole night. Each event was filtered using a Hilbert transform in two ways: first, in the SO frequency band to extract the instantaneous phase time series, and second, in the sigma frequency band to extract the instantaneous amplitude time series. A 2-sec buffer was included on either side of the signal for each SO event to avoid filter edge artefacts; the buffer was discarded after filtering. Each filtered event was then binned (18 bins) and the amplitude in each bin was averaged across all events into a single, grand average phase-amplitude time series which was submitted for MI analysis. Raw MI values were log-transformed to better capture harmonic proportions of neural oscillatory activity across lower to higher frequencies (c.f., Buzsáki & Draguhn, 2004; Penttonen & Buzsáki, 2003), and to improve normality within the data. As a result of this transformation, given that raw MI is a value from 0 to 1, greater log-transformed MI is indicated by a value that is less (vs. more) negative, with a lower limit of -∞ and an upper limit of 0.

Preferred coupling phase was quantified from this same grand average phase-amplitude time series by extracting a measure of circular mean direction to reflect the preferred SO phase (in radians) of maximum sigma power amplitude. Like the MI, a single value was produced for each participant on each night. We arranged our coupling phase analysis such that the depolarizing SO up-state was positioned on the circular/polar plot at 270°, and the hyperpolarizing SO down-state was positioned at 90° (See Figure 2C). Rather than using the raw coupling phase values, our analysis instead focused on a transformed value of coupling phase distance from the SO up-state. This variable, used in our linear regression models to

predict memory consolidation scores (see below), was derived using the following steps. First, each participant's raw coupling phase value (on a scale of 0-360°) was subtracted from a common reference point of 270° (i.e., the up-state). Second, resulting values were then re-scaled by subtracting 360 from difference scores > +180° and adding 360 to difference scores > -180°, which placed all scores on a range from -180° to +180°, now reflecting a distance either before or after the up-state. Due to outliers and poor distributional qualities (e.g., skewness), the absolute value of this score was then taken, whereby larger values reflect a distance further away from the up-state peak, but do not indicate in which direction (before vs. after). Hereafter, this transformed absolute coupling phase distance variable is referred to simply as CP. This measure is similar to one used in a study of SO-spindle CFC and memory in children and youth (Hahn et al., 2020), however the measure derived from their method reflected the proportion of spindles (among all spindles) that occurred within a specific range around the SO up-state peak.

Measures of MI and CP, derived during a combined N2+N3 stage of all-night sleep, were compared between baseline and learning nights to examine any significant changes after completing the word-pair task. Coupling measures were then examined for associations with memory consolidation, using relative change in MI and CP between the two nights, calculated as: [(learning night) – (baseline night)], and referred to as relative MI (rel_MI) or relative CP (rel_CP). In turn, rel_MI reflects an increase or decrease in coupling strength between nights, and rel_CP reflects a shift in distance from the SO up-state between nights (i.e., closer to or further from the up-state). These same examinations of CFC between nights and in association with memory were also performed for data from stage N2 and N3 sleep considered separately (see Supplemental Results).

Statistical Analyses

Data Screening

Data for the primary demographic, cognitive testing, and CFC (MI, rel_MI, CP, rel_CP) measures of interest were screened for univariate outliers, and adherence to statistical assumptions of normality, homogeneity of variance, and linear relationships. Univariate outliers were screened by visual inspection

of box-plots, and formally identified by inspecting z-score frequency tables for values +/- 3 SD from the mean. Normality was examined using measures of skewness and kurtosis, using a Shapiro-Wilks test, and by visual inspection of histograms, Q-Q plots, and box-plots. Normality of the deviation scores (X – *mean*) of each variable was also examined using similar methods. Homogeneity of variance was examined using Levene's test for each repeated-measure variable pair. Linearity was examined by inspecting bivariate scatterplots between primary predictor and outcome variables.

There were no univariate outliers across any of the main demographic, cognitive testing, and CFC variables on either night. A positive skew and significant Shapiro-Wilks test ($p = 0.003$) in the AHI covariate is unsurprising given that most participants had an AHI < 10; this was corrected with a Log10 transformation. Homogeneity of variance was confirmed using a Levene's test with each pair of repeated-measures variables (MI, CP). Conversely, 2 outliers were found in our variable reflecting relative change in MI (rel_MI); a consensus was reached to remove data points identified as outliers and conduct analyses with these variables using a trimmed sample (n = 23 or 24), which improved this variable's distributional qualities (i.e., skewness, normality). Supplemental CFC variables were similarly screened, and outliers were also removed; however, most of the Cz-measured variables (rel_MI, CP, rel_CP) displayed skewness and non-normality that was only partially improved after removing outliers. The pattern of results was largely similar among analyses with the full sample.

Between-Night Comparisons

To address our first study aim, we tested for between-night differences in SO – σ CFC using a one-way, within-subjects analysis of covariance (ANCOVA). Differences between nights in MI and CP were examined separately. Recording night (baseline vs. learning) was a repeated-measures factor. Age was included as a covariate, as well as apnea-hypopnea index (AHI; measured on the baseline night, log-transformed), to account for added variability due to sleep apnea severity. *Post-hoc t*-tests were examined following a significant main effect or interaction. We also quantified the stability of MI between experimental nights using Pearson's correlations.

Associations between MI and CP with Word-Pair Memory

To address our second study aim, associations between CFC and memory were tested using hierarchical multiple regression, with age and log-AHI included in Step 1, and the CFC measure of interest in Step 2. The CFC model predictor we used was a difference score (learning night – baseline night) reflecting the relative (individual) change between study nights in measures of MI and CP. Each measure was entered in separate regression models, to examine whether change in coupling strength or coupling phase distance from the up-state can predict overnight memory consolidation scores. The R^2-change and F-scores of the model were examined alongside regression coefficients to determine the effects of each CFC variable in predicting word-pair performance. Absence of multicollinearity among predictors was also verified during data screening.

Exploratory Analysis: MI x CP Interaction

Lastly, we conducted an exploratory analysis to examine potential interaction or moderation effects between SO – σ MI and CP in predicting memory scores. To accomplish this, MI, CP, and their interaction were each entered in a hierarchical regression model. The interaction was created by deriving the product of the mean-centered MI and mean-centered CP values. In contrast to our main analyses above, which examined measures of relative change in coupling between nights, our exploratory interaction model focused on CFC data measured from the learning night only. The MI-by-CP product term was entered in a regression model like those described above, with age and AHI entered at Step 1. At Step 2, the mean-centered main effect variables (MI, CP) plus the interaction (product) term were added to the model, and we examined R^2-change and F-scores alongside regression coefficients. On detecting a statistically significant interaction, follow-up analyses examined the simple slopes of regression weights for the predictor variable (CP) at different levels of MI, which was treated as the moderator variable. For this step, two follow-up analyses were performed using the same regression approach, guided by the steps outlined by Meyers et al. (2013): The first follow-up analysis repeated the base interaction model after the centered MI variable was re-centered to reduce all values by 1 SD unit ("Low MI"), and the second follow-up repeated the base interaction model after the centered MI variable

was re-centered to increase all values by 1 SD unit ("High MI"). Follow-up analyses determined if the relationship between CP and memory consolidation changes with higher or lower coupling strength.

Correction for Multiple Comparisons

A Bonferroni method was used to adjust our critical *p*-value to account for the number of analyses being performed using our primary independent measures. Each CFC variable (MI, CP) in our primary analyses on Fz were examined for between-night differences and associations with word-pair memory consolidation. In turn, four primary analyses were conducted, resulting in an adjusted *p*-value of (.05 / 4 = .0125 = .013). Our exploratory analyses were evaluated with a more liberal criterion of $p < .05$.

Results

Sample Characteristics and At-Home Screening

Participant demographics and eligibility screening results are presented in Table 1. Participants (*M* [*SD*] age = 69.12 [5.53]) were modestly balanced in terms of sex (64% female) and were mostly French-speaking (80%) and right-handed (80%). Years of education ranged from 12–26 (*M* [*SD*] = 16.78 [3.50]) years. Participants maintained overall good-quality sleep between study nights, as reflected by the average sleep efficiency from their daily sleep diary (*M* = 84.36%) and wrist actigraphy (*M* = 77.88%).

Behavioural Data

Participants completed pre-sleep (PM) and post-sleep (AM) cognitive testing on their second recording visit. On the 40-item word-pair memory task, participants recalled an average of 28.12 (*SD* = 7.12; range = 13–38) correct word-pairs on the PM cued-recall test, and an average of 26.16 (*SD* = 7.76; range = 11–39) correct word-pairs on the AM cued-recall test. The overnight (pre-sleep to post-sleep) absolute change in recall performance ranged from forgetting 6 word-pairs to remembering an additional 3 (*M* [*SD*] = -1.96 [2.44]; *Med* = -2; *Mode* = -1). The difference in performance between PM and AM recall tests was statistically significant ($t(24) = -4.015$, $p = .001$. The Overnight Consolidation score, reflecting the total number of correct word-pair responses involving the *same* word-pairs between PM and AM recall tests, ranged from 9 to 38 across the sample (*M* [*SD*] = 24.88 (7.93)).

Sleep Parameters

Sleep Architecture

Table 2 presents sleep architecture and other basic sleep parameters from the first (baseline) and second (learning) study nights. Participants achieved slightly higher sleep efficiency ($t(24) = -2.472$, $p = .021$) on the learning night versus baseline.

Discrete SO and Spindle Events

Presented in Table 3 are descriptive statistics and simple between-night comparisons of event-detected slow oscillations (SO) and sleep spindles from Fz during all-night N2+N3 sleep. There was a general trend for SO and sleep spindle activity to either remain stable or to decline (spindle peak-to-peak amplitude) between baseline and learning nights.

Specific Aim 1: SO – σ CFC During Sleep After Learning in Healthy Older Adults

Presented in Table 4 are descriptive statistics and between-night comparisons for coupling strength (MI) and coupling phase distance from the up-state (CP). Coupling dynamics across study nights are depicted in Figure 2. Coupling strength was not statistically different between nights (F (1, 22) = 3.252, $p = .085$). Similarly, CP did not significantly differ between nights (F (1, 22) = 3.784, $p = .065$).

Specific Aim 2: SO – σ CFC and Overnight Memory Consolidation

As presented in Table 5 and Figure 3A, regression models indicate that rel_MI was not significantly associated with memory performance in this sample. However, a greater relative decrease in our transformed CP variable (reflecting a shift in coupling phase *towards* the up-state) was predictive of better memory consolidation (F (3, 21) = 5.732, $\Delta R^2 = 0.278$, $p = .005$; *B(SE)* = -0.108 (0.033), $\beta = -.569$) (Table 5, Figure 3B).

Exploratory Aim: Interactions Between MI and CP and Relations with Memory

Results from our exploratory interaction models are presented in Table 6. A model containing SO – σ MI, CP, and their interaction significantly predicted memory consolidation scores (F (5, 19) = 4.399, $\Delta R^2 = 0.362$, $p = .008$). In the model itself, significant associations with memory were found for both the MI x CP interaction (*B(SE)* = -0.043 (0.019), $\beta = -.384$, $p = .033$), and for the CP main effect (*B(SE)* = -0.102 (0.031), $\beta = -.680$, $p = .004$). Inspection of partial correlations suggest that the correlation with

memory was strongest for CP (r = -.596). Follow-up analyses repeated the regressions with MI re-centered to reduce values by 1 SD unit, and again with MI re-centered to inflate values by 1 SD unit. Follow-up analyses revealed that CP closer to the SO up-state remained a significant predictor of memory alongside the interaction when MI was shifted upward (i.e., reflecting greater coupling strength; β = -.978, p = .001), but was no longer a significant predictor after MI was shifted downward (i.e., reflecting less coupling strength; β = .381, p = .120). Inspection of partial correlations when the MI moderator was higher suggested that the association between memory and CP was even stronger than in the base model (r = -.654). See Figure 4 for a plot showing the simple slopes of these moderator analyses.

In summary, MI remained stable between recording nights, and the individual (relative) change in coupling strength was not predictive of memory. Similarly, our measure of absolute distance in coupling phase from the SO up-state remained stable between nights, although a relative shift in CP towards the up-state after the learning task predicted better overnight memory consolidation. However, based on our examination of interactions between the two, our results suggested that the predictive effects of a coupling phase closer to the up-state peak is enhanced when accompanied by higher (vs. lower) coupling strength.

Discussion

The aim of this study was to examine CFC during NREM sleep and its association with learning and memory consolidation in healthy older adults, with a focus on phase-amplitude coupling between SO and slow spindle (sigma) activity (9–13 Hz) on the frontal midline (Fz). Our first main hypothesis that SO – σ CFC would increase from baseline after participants complete a pre-sleep learning task was not supported, as there was no difference between baseline and learning nights in our measure of MI or in our transformed measure of absolute coupling phase distance from the SO up-state (CP). Our second hypothesis that greater MI is positively associated with memory was not supported, although our hypothesis that a coupling phase closer to the SO up-state is associated with memory was supported. Specifically, using multiple regression, our data suggests that a relative shift from baseline in coupling phase towards (vs. away from) the SO up-state after learning is predictive of better memory consolidation. Together, our measures of coupling strength and phase distance from the up-state were not

affected on the group level by a pre-sleep learning experience, however individuals whose coupling phase shifted closer to the up-state after learning appeared to retain more word-pairs after overnight sleep. Lastly, an exploratory interaction model between MI and CP during post-learning sleep suggested the association between a coupling phase closer to the up-state and better memory consolidation is facilitated or blunted by higher versus lower coupling strength, respectively.

Current State of the Literature: A Comment on Research Standardization

Compounding evidence from multiple correlational and experimental studies (mostly with young adults) has contributed ample support for the idea that more precise SO-spindle CFC is associated with better sleep-associated memory consolidation. However, there are noticeable differences in experimental and analytic methods across these studies that are important to consider when reviewing the currently available data. We highlight and discuss a selection of these differences below.

Most available studies of CFC and memory report data from overnight sleep, while some studies report data from a daytime nap (Bar et al., 2020; Ladenbauer et al., 2017, 2021; Ruch et al., 2012; Schreiner et al., 2021), or from an evening nap (Göldi et al., 2019). Given the known circadian factors that influence both sleep regulation (e.g., Borbély & Achermann, 1999; Dijk & Lockley, 2002) and brain oscillation activity (e.g., Bódizs et al., 2022; Schalkwijk et al., 2019), studies of NREM SO – σ CFC from overnight sleep may not be equivalent to studies of SO – σ CFC from a daytime nap. Further, there is wide variability in the memory task studies employ. Broad distinctions can be drawn between studies of only declarative/episodic (e.g., Helfrich et al., 2018; Niknazar et al., 2015) or procedural memory (e.g., Bartsch et al., 2019; Cox et al., 2018), and studies that examine both (e.g., Ladenbauer et al., 2017; Mikutta et al., 2019). More fine-tuned differences include the type of training (e.g., 1-2 list exposures or practice rounds [e.g., Mölle et al., 2009; Ngo et al., 2013] vs. learning to a criterion [e.g., Bar et al., 2020; Helfrich et al., 2018; Zhang et al., 2020]), and the type of memory being tested (e.g., emphasis on recognition [such as old vs. new; e.g., Cairney et al., 2018; Helfrich et al., 2018] vs. cued recall [e.g., Ngo et al., 2013; Schreiner et al., 2018] vs. a mix of both [Muehlroth et al., 2019]). The number of test items (i.e., single words, word-pairs, word-nonsense word pairs, scene-image pairs) also varies. For example,

studies of declarative memory have used tasks with 15 (Mikutta et al., 2019), 40 (e.g., Ladenbauer et al., 2017), and 120+ test items (e.g., Mölle et al., 2011; Ngo et al., 2013). A study of ageing (Muehlroth et al., 2019) exposed seniors to fewer memory items on a scene-word memory task, as well as an additional learning opportunity, relative to young adults. Further research is needed to determine if and how the learning load of a specific pre-sleep memory task influences or moderates subsequent NREM CFC.

Studies also vary in researcher-based pre-processing and analysis decisions, including which sleep stage is examined (N2 vs. N3 vs. N2+N3). Most EEG studies examine data near the scalp midline but differ in using frontal versus central versus parietal channels, or in using single versus multiple channels (i.e., cluster-based analyses). Regarding frequency bands, many studies use a fixed fast spindle band in the range of 12–16 (+/-1) Hz (e.g., Cairney et al., 2018; Clemens et al., 2011; Helfrich et al., 2018; Mikutta et al., 2019; Mölle et al., 2009; Staresina et al., 2015). Studies examining slow spindle activity may use a band in the range of 8–13 (+/-1) Hz (e.g., Cairney et al., 2018; Clemens et al., 2011; Klinzing et al., 2016; Mölle et al., 2011; Muehlroth et al., 2019; Yordanova et al., 2017). Still others employ a wider, more general band (e.g., 10–16 (+/- 1) Hz, Mak-McCully et al., 2017; Ruch et al., 2012; Zhang et al., 2020). More recent studies have employed individually adapted frequency bandwidths (e.g., Cox et al., 2018; Dehnavi et al., 2021) or amplitude thresholds (Muehlroth et al., 2019). Differences in CFC analysis include what data is analyzed (e.g., all SOs vs. SO-spindle complexes), and which measures are derived (e.g., coupling phase, coupling strength [e.g., MI vs. mean vector length], time-frequency representations). Thus, variation in researcher-based decisions could also cloud study comparability.

Taken together, evidence is accumulating for relations between precise SO – σ CFC and better memory, however the studies examining this can differ in important ways that merit consideration when synthesizing the available data. As this research area continues to develop, it will be important to unify and establish specific taskforce guidelines on CFC measurement to facilitate research standardization, improve measurement reliability, and allow for 'meta-analysis-friendly' reports to aide research synthesis.

SO – σ CFC Between Baseline and Learning Nights

SO – σ coupling strength (MI; Tort et al., 2010) and coupling phase distance from the up-state (CP) were both stable on average across the two experimental recording nights, as reflected by a lack of between-night differences, and by sufficient correlations of each measure between nights. The group-level phase-amplitude relationships observed in this study are consistent with previous findings that slower (frontal) spindle/sigma power is more synchronized with the SO up-to-down-state transition (e.g., Klinzing et al., 2016; Helfrich et al., 2019; Muehlroth et al., 2019; Ngo et al., 2013; Yordanova et al., 2017). Our supplemental analyses also show that none of the additional coupling measures (MI, CP, or raw coupling phase, from all SO events or from SO sub-groupings) evidenced a significant difference between nights on either channel. Together, these results do not support a hypothesis that SO – σ CFC is modulated at the group-level by pre-sleep declarative learning, at least for coupling with slow sigma activity in older adults. Although, it is also possible that our learning task was not challenging or demanding enough to influence this type of brain activity to a noticeable degree. In turn, the current study adds to a mixed literature about relations between coupling strength and sleep-associated memory consolidation. Specifically, while several studies have reported associations between coupling strength and procedural or non-declarative memory (e.g., Bartsch et al., 2019; Hahn et al., 2022; Mikutta et al., 2019), fewer studies have reported positive associations between coupling strength and declarative memory (e.g., Hahn et al., 2020; see also Ladenbauer et al., 2017, and Dehnavi et al., 2021), and some others report no association between coupling strength and declarative memory (e.g., Denis et al., 2022; Helfrich et al., 2018; Ladenbauer et al., 2021; Mikutta et al., 2019; Niknazar et al., 2015; Zhang et al., 2020). Conversely, multiple studies have reported that pre-sleep learning and overnight memory consolidation is more reliably associated with measures of SO – σ preferred coupling phase (e.g., Helfrich et al., 2018; Mikutta et al., 2019; Muehlroth et al., 2019; Niknazar et al., 2015; Zhang et al., 2020).

Our results of between-night comparisons are more in-line with an alternative hypothesis that, like spindles (Cox et al., 2017; De Gennarro et al., 2005) SO – σ CFC is a stable, trait-like individual difference. Indeed, Cox and colleagues (2018) demonstrated that SO phase of maximum spindle power/amplitude differed slightly across individuals, between N2 and N3 stages, and between anterior

and posterior scalp regions, but remained stable across two consecutive nights. As well, Bastian and colleagues (2022) recently demonstrated that SO – σ CFC, in both fast- and slow-spindle ranges, did not differ between an experimental night with a pre-sleep spatial memory task versus a non-learning control recording. Hahn and colleagues (2022) also showed that SO-spindle coupling strength was highly correlated between an adaptation night and a learning task night.

SO – σ CFC Predicting Sleep-Associated Declarative Memory Consolidation

Spindle activity is hypothesised to facilitate synaptic long-term potentiation and strengthen newly acquired memory traces (Fernandez & Lüthi, 2020). A recent meta-analysis (Kumral et al., 2022) showed that spindles are associated with both declarative and procedural memory tasks but may in fact have a stronger association with procedural tasks. Emerging research examining NREM CFC suggests that spindle frequency activity, properly timed to the SO up-state, is most optimal for supporting memory consolidation (e.g., Mikutta et al., 2019; Mölle et al., 2009, 2011; Niknazar et al., 2015; Ruch et al., 2012). Further, the amplitude of hippocampal (HC) ripples (e.g., 80–100 Hz) can be modulated by spindle (e.g., 12–14 Hz) phase, and both in turn are associated with the SO phase (Amiri et al., 2016; Clemens et al., 2007; Helfrich et al., 2019; Latchoumane et al., 2017; Ngo et al., 2020; Staresina et al., 2015). Evidence is growing for an "active systems consolidation" model of memory consolidation. This model posits that neural representations (or, engrams) of recently encoded experiences in both neocortical and HC networks are repeatedly co-reactivated during NREM sleep, which promotes consolidation across time by reorganizing and integrating memory traces from (temporary) HC stores into existing and HC-independent cortical networks; the precise coupling of NREM SOs, spindles, and ripples is considered a core neural mechanism of this "corticalization" process (e.g., Geva-Sagiv & Nir, 2019; Helfrich et al., 2019; Klinzing et al., 2019; Mölle & Born, 2009; Muehlroth, Rasch, & Werkle-Bergner, 2020; Rasch & Born, 2013). Enhanced CFC may signal a relative increase in functional connectivity during or after a learning period, and perhaps so across domain-specific (e.g., verbal, visual) cortical regions (c.f., Yordanova et al., 2017). Importantly, many discussions about SO – σ CFC and memory emphasize the role of this triple SO-spindle-ripple phase-locking in the context of centro-parietal fast spindle activity;

conversely, evidence for a potential role of CFC with frontal slow spindle activity in overnight memory consolidation is less consistent. In turn, a principal finding in this study was of an association between coupling phase distance from the up-state with memory consolidation in the context of CFC in the slow spindle range (9–13 Hz) among older adults.

Coupling strength, measured as a relative change score between nights (Primary Results) or examined on each night separately (Supplemental Results), was not associated with memory consolidation. Supplemental analyses with rel_MI from SO+spindle events on Cz suggested that a greater increase in coupling strength after learning predicted worse memory. Overall, results from our analyses between coupling strength and memory were generally opposite to expectation. Measures of coupling strength are reported in several studies of CFC and memory, although some (e.g., Niknazar et al., 2015) have proposed that SO – σ coupling phase near the up-state may be a stronger predictor of memory.

While our measures of raw coupling phase did not correlate with memory in this study (Supplemental Results), our transformed variable of coupling phase distance from the SO up-state (CP) did. Specifically, primary analyses with rel_CP (N2+N3, Fz) suggested that older individuals whose SO – σ coupling phase shifted *towards* the SO up-state consolidated more word-pair associations relative to those whose CP shifted further *away* from the up-state. A similar association was found in our supplemental analyses with rel_CP from isolated SO events not joined with a spindle (SO(-) – σ, N2+N3, Fz). However, the same effect was not observed with SO+spindle events, or with any CP measure from Cz (Supplemental Results). The lack of results from our Cz channel could be due to the limited variability in CP on Cz within and between nights, relative to Fz, or due to the skewed distributional qualities of measures from Cz. Collectively, these results support an argument that potentially important distinctions in coupling dynamics likely exist when measures are derived from isolated versus naturally co-occurring events, or from all SO events.

SOs and spindles are distinct oscillatory events that can appear in isolation but are also known to spontaneously co-occur (Hahn et al., 2020; Oyanedel et al., 2020; Schreiner et al., 2021). Studies that examined SO – σ CFC in the context of co-occurring SO-spindle complexes in humans (e.g., Helfrich et

al., 2019; Hahn et al., 2020; Klinzing et al., 2016; Muehlroth et al., 2019; Niknazar et al., 2015; Schreiner et al., 2021) and rats (e.g., Oyanedel et al., 2020) highlight the potential importance of leveraging the natural co-occurrence of neural oscillations when studying measures of CFC. For instance, Oyanedel and colleagues (2020) showed that ripple (150–250 Hz) power enhancement around the SO up-state was strongest among SO events that co-occurred with a spindle versus isolated SOs, and that power suppression during the SO down-state was strongest among isolated SOs. To our knowledge, there is a paucity of studies which examine CFC among SO-spindle complexes in older adults and in the context of memory, and of studies drawing comparisons between CFC measures derived between SO(+) and SO(-) events in this age-group. The difference in outcome between SO sub-groups (e.g., relatively greater amplitude modulation on SO(+) events) also highlight that sigma spectral power is a proxy of spindle activity, and that sigma power dynamics may differ when in the presence or absence of a detectible spindle event. Such differences may have unique functional properties, signal-processing considerations, and associations with memory.

Together, our study with healthy older adults suggests that a slow spindle coupling phase closer to the SO up-state is predictive of better memory, but only on the frontal channel, and only in the context of a combined N2+N3 sleep period. This finding is intriguing given the emphasis that has been placed on memory-related benefits of SO-coupling with fast (relative to slow) spindle power in previous studies, mainly with young adults (e.g., Helfrich et al., 2018; Mölle et al., 2011; Muehlroth et al., 2019). Our main analyses yielded statistically significant associations between CP (measured from Fz) and memory during a combined N2+N3 sleep stage, while our supplemental analyses with each stage examined separately did not yield similar results. The dynamics and properties of SOs and spindles may differ across the two NREM stages (N2 and N3). For example, the extent or magnitude of spindle power synchronizing to the SO phase could differ between lighter and deeper NREM sleep (c.f., Cox et al., 2018), which may have resulted in weaker associations with memory in this sample when stages were examined separately. Alternatively, perhaps there was not enough statistical power to detect an effect using data from each stage separately, compared to using data from the combined sleep stage; this speaks to the need for

replicating our analyses with a larger sample. Results with relative change in CFC further suggest that individual-level differences in coupling dynamics may be an important factor to consider when examining SO – σ CFC and memory (e.g., differences in brain activity profiles between participants whose coupling phase shifted towards, versus away from, the up-state after learning), and this variability may be especially relevant in research with older adults.

Two recent studies of SO – σ CFC during overnight sleep (Helfrich et al., 2018; Muehlroth et al., 2019) provide evidence that less precise timing of SO and spindle activity with ageing is associated with reduced grey matter volume in the medial PFC, and with worse declarative memory performance. While both studies examined fast spindle power on central EEG channels, Muehlroth and colleagues (2019) also examined coupling with slow spindle power on frontal (F3 and F4) channels. Muehlroth and colleagues described that a "youth-like" SO-fast spindle coupling pattern, with a peak at or just after the up-state, is associated with better memory retention, and greater medial-pre-frontal and thalamic grey volume; the older adults with a "youth-like" coupling pattern did better on memory testing, whereas older (and younger) adults with a more "aged" pattern (fast spindle activity peaking too early before the up-state, stronger slow spindle power increases between the up-state and down-state) showed worse memory. Muehlroth and colleagues (2019) suggest that slow spindles may not be effective in HC-dependent memory consolidation and may be more reflective of cortico-cortical communication rather than HC-thalamic-cortical communication. Slower spindle power (from Fz) in our study tended to peak after the up-state, during the up-to-down-state transition, and faster spindle power (from Cz; Supplemental Results) tended to peak before or during the up-state, which is consistent with previous reports (e.g., Mölle et al., 2011; Muehlroth et al., 2019). However, inspection of our data showed that this was not true for everyone, as 2 participants' coupling phase was locked before the up-state on Fz, and 1 participant's coupling phase was locked after the up-state on Cz. Our finding of rel_CP shift towards the up-state on Fz and better memory could reflect the more "youth-like" properties of these individuals' brain activity, relative to those whose CP shifted away from the up-state. Examining this further would be aided by a study with samples of "younger" older and "older" older adults, alongside a young adult control group.

In considering that measures of coupling strength and coupling phase are reflections of the same underlying construct, we also conducted an exploratory analysis to examine potential interaction effects between SO – σ MI and CP in predicting memory consolidation. A regression model containing the mean-centered MI, CP, and MI x CP interaction variables significantly predicted word-pair overnight consolidation scores in our sample of healthy older adults. Follow-up moderation analyses suggested that the association between coupling phase closer to the up-state and memory consolidation was enhanced when coupling strength was higher, and diminished when coupling strength was lower. Again, this effect was found only with slower spindle activity from Fz and was not seen with faster spindle activity from Cz (Supplemental Results). This may be interpreted as indicating that the memory-enhancing effect of SO – σ coupling strength is contingent on the timing of spindle activity with respect to the SO; stated differently, greater coupling strength alongside poorly timed spindle power increases may merely result in stronger "bad" coupling, which may impede HC-neocortical transactions. These interaction effects should be interpreted cautiously given our small sample size, but the results provide an interesting perspective about interpreting the functional significance of one type of coupling measure (e.g., coupling phase) in the context of the other (e.g., coupling strength), rather than separately. Relatedly, Ohki (2022) has recently described a novel measure that considers both amplitude and phase position data in examining phase-amplitude coupling. Given the significant memory associations with our coupling phase distance variable and its interaction with coupling strength, we provide evidence that the two measures may have unique functional contributions to memory. It would be interesting if any interacting effects on memory between MI and CP change across the lifespan, however testing this would require a larger sample and a young adult control group.

SO – σ CFC and Lifespan Ageing

An important contemporary research topic is of examining age-related declines in CFC, and how this could account for memory impairments with ageing. Most available studies examining CFC during sleep, in or outside the context of memory, report on data from young adults. Both SO and spindle activity declines with older age (e.g., Carrier et al., 2011; Martin et al., 2013), and some evidence

suggests the same is true for SO – σ CFC. In the context of development, SO – σ CFC was shown to increase from childhood to adolescence across a 7-year follow-up (Hahn et al., 2020). However, similar longitudinal research is lacking in the context of ageing. Ageing-related frontal and thalamic deterioration and impaired SO-triggered spindles are two mechanistic explanations for SO – σ "de-coupling" seen with ageing (e.g., fast spindle activity peaking out of time with the SO up-state in older versus younger adults; Helfrich et al., 2018; Muehlroth et al., 2019). Disrupted TC network integrity with older age could also impair NREM coupling, and in turn, sleep dependent memory consolidation.

The present study did not have a young adult comparison group, and thus could not examine age-group differences in CFC. Nevertheless, findings show that SO – σ coupling phase distance closer to the up-state is positively associated with memory in older adults, suggesting that coupled brain activity continues to facilitate sleep-associated memory processes in older age. However, this requires more investigation in studies directly comparing younger and older adults. Further, cross-sectional comparisons between younger and older groups can only provide so much information about age-related changes or declines in coupling strength and coupling phase. A prospective longitudinal design is needed to study long-term changes in both coupling measures and their relations with memory.

Our results must also be interpreted considering the analytical decisions made, and in relation to what is known about NREM oscillations and ageing. Chiefly, one of the primary components in measuring SO – σ CFC is the data derived from detected SO events. Our SO detector was based on Staresina and colleagues (2015) and utilized an adapted amplitude thresholding procedure applied to candidate SOs that met other criteria. In turn, this detection finds the largest slow waves for each participant and recording, which is optimal considering the reduced amplitude of slow waves often seen in seniors (c.f., Webb & Dreblow, 1982). This can be compared with other slow wave detection methods with a fixed amplitude threshold (e.g., peak-to-peak amplitude $\geq$ 140 μV; Massimini et al., 2004). However, based on recent research in animals (Kim et al., 2019), there may be functional differences in oscillation activity between SO (e.g., < 1 Hz) and delta (e.g., 1 –4 Hz) bands in relation to memory (i.e., facilitating retention vs. forgetting). Accordingly, it is important to consider the difference in numbers and

characteristics of SOs found among different detectors. Together, these points about SO detection echo conclusions from recent reviews (Muehlroth & Werkle-Bergner, 2020; Muehlroth, Rasch, & Werkle-Bergner, 2020) that stressed the importance of designing "age-fair" studies when examining ageing. Changes with age in oscillation activity (e.g., reduced amplitude or frequency) should not be ignored in studies that include data from older adults.

Study Limitations and Strengths

There are several limitations of this study that merit consideration. First, while this study examined relative change in CFC between a learning night and a non-learning baseline, the baseline was also the first screening night. It is possible this first recording visit was sub-optimal as a baseline because, for most participants, this was their first experience in a sleep lab and with the recording equipment (i.e., new sights, sounds, sensations). In turn, it is possible the lack of differences in CFC measures between nights could also be explained by the added "learning" involved on the (first) PSG night. Sleep architecture was largely similar on both nights, however participants achieved better sleep efficiency on Night 2 (average SE% = 83.26% vs. 85.71%). Thus, we cannot rule out the influence of a possible first-night-effect without a study that includes at least 3 recording nights. It remains to be established if sleep micro-architecture (including CFC) is susceptible to first-night effects like sleep macro-architecture. Importantly, our supplemental analyses demonstrated that the association between CP and memory was specific to the second (learning task) night, whereas there was no association found between CP and memory on the first night. There were no differences in our main CFC variables or our secondary variables (detected events, PSD) between nights, except that spindle peak-to-peak amplitude decreased on the second (learning) night. While we can only speculate about why spindle amplitude alone was greater on Night 1, it is possible that this reflects a learning effect from the overall novelty of participants' first recording visit (e.g., sleeping in our lab, experiencing the equipment set-up, receiving instructions for at-home sleep monitoring). Alternatively, greater spindle amplitude on the first visit could reflect a relative enhancement of underlying TC network activity associated with extra sensory gating in response to the novel sleep lab experience (e.g., unfamiliar bedroom, wearing the recording equipment while sleeping;

Fernandez & Lüthi, 2020; Schabus et al., 2012). Second, and relatedly, our baseline night did not include any control task. A control task that requires similar cognitive engagement would provide a more refined test of how learning might influence coupling dynamics. Third, our sample may have been underpowered, and included participants with a range of sleep apnea severity. While this may help enhance our study's generalizability, and our analyses included AHI as a covariate, the deleterious effects of sleep apnea on sleep continuity and stability could have introduced extraneous variance and impeded some subjects from achieving deep enough sleep for optimal slow wave activity to occur (e.g., higher sleep fragmentation). Our research team is currently completing data collection for a follow-up study that addresses each of these limitations, by including 3 recording nights, a cognitive control task, and stricter limits for sleep apnea severity, as well as a young adult control sample to examine age-group differences.

Aside from these limitations, this study has noted strengths. First, participants were recruited and selected using stringent *a priori* criteria that required them to satisfy thresholds on screening tests of cognitive functioning, and across a battery of self-report questionnaires. Second, the word-pairs selected for the memory task were carefully chosen and constructed using specific criteria about word length and frequency, and considering the emotionality of included words. It is also important to note that our word-pair associates task used a cued-recall test, which is different from earlier and often-cited studies of NREM CFC and memory in older adults (Helfrich et al., 2018; Ladenbauer et al., 2017; Muehlroth et al., 2019) that placed more emphasis on tests of recognition memory. Third, CFC was computed using data from both nights of sleep, allowing for an examination of relative change in CFC after learning. Fourth, our analysis methods are in-line with current recommendations for deriving measures of CFC (e.g., computing CFC measures from detected oscillatory events; c.f., Aru et al., 2015). Finally, and overall, this study capitalized on available data by providing a comprehensive analysis of coupling dynamics during NREM sleep in our sample of healthy older adults.

Conclusion

Results of our study with older adults suggest that measures of SO – σ coupling strength and coupling phase do not reliably change between a baseline and a learning condition, but that memory

consolidation may be facilitated by a shift in coupling phase towards the SO up-state. Moreover, our exploratory interaction model revealed, to our knowledge, a novel finding that the strength of association between coupling phase closer to the up-state and better memory may be enhanced when accompanied by greater (vs. weaker) coupling strength. This study builds on and extends previous work by (1) examining SO – σ CFC after a pre-sleep learning task, and as a measure of relative change from a non-learning baseline; (2) examining associations with memory using a transformed measure of coupling phase distance from the up-state; and (3) examining the interactive effects between SO – σ coupling strength and coupling phase distance.

Supplementary Material

Supplementary Methods

Detection of Co-Occurring SO-Spindle Complexes

The occurrence of overlap between detected SO and spindle events was obtained using a specialized script function in our in-house analysis tool. This script identified moments in the EEG recording where a detected SO and a detected spindle overlapped by at least 25%. It is important to note that the script function did not anchor spindle overlap to any particular SO phase. Each overlapping event was relabelled as SO(+) events, and remaining SOs that did not meet the overlap criteria were labelled as SO(-). These overlapping (SO(+)) and non-overlapping (SO(-)) events were then examined for SO – σ CFC and associations with learning and memory as described in the main paper.

Raw SO – σ Coupling Phase

Supplemental analyses present between-night differences in raw coupling phase (circular metric; see CFC section of main Methods). Differences between nights were examined using a Watson-Williams test for means in a circular distribution, using a permutation shuffling method (10,000 permutations) to facilitate within-subjects/repeated-measures comparisons (Watson & Williams, 1956; see also Berens, 2009). Watson-Williams tests were only conducted on circular data where a preliminary Rayleigh test (Fisher, 1995) verified the presence of a preferred mean coupling direction (vs. uniform distribution) on both nights. Circular-linear correlation analyses examined relations between the raw coupling phase on the learning night and word-pair overnight memory consolidation, using measures derived from both (Fz and Cz) channels.

Analyses Across Nights, and in N2 and N3 Sleep Stages.

Two exploratory analyses further examined relations between CFC and memory in our study. The first analysis repeated our hierarchical regressions with the primary (MI, CP) variables taken from the same combined N2+N3 sleep stage but using measures derived from each night separately (Baseline, Learning), instead of using a measure of change between nights. The second analysis repeated each of our primary statistical analyses with all SO events but using CFC data derived from N2 and N3 sleep stages

considered separately; this included examining between-night differences in MI, CP, and raw coupling phase, as well as associations with memory (rel_MI, rel_CP, raw coupling phase). Analyses were performed on data from both Fz and Cz.

Power Spectral Analysis

Power spectral density (PSD) analysis was performed using a Welch periodogram method with overlapping segments (50% overlap) and a 4-second Hanning window filter. Standard spectral bandwidths were applied to extract measures of PSD from frontal and central EEG recording channels in the SO (0.5–1.25 Hz) and sigma range (fixed at 9–13 Hz [Fz] or 12–16 Hz [Cz]). A Butterworth filter passed through the data twice to minimize phase-shifting. PSD values on each night were extracted as values following normalization to the spectrum integral, which reflects the average of the total signal (e.g., Fell et al., 1996; Vysata et al., 2012).

Supplementary Results

S.1. Analyses on Cz, and Examinations of Raw Coupling Phase and SO Sub-Groups

The following sections present similar analyses to the main study aims above, using complementary datasets of coupling strength and coupling phase (raw score and transformed variable) derived from all detected SO events, and from SO sub-groups of overlapping SO-spindle complexes (SO+spindle; SO(+)) versus isolated SO events (SO-spindle; SO(-)). Distinctions are made when relevant between results from channels Fz or Cz. Analyses on Cz focused on CFC with fast spindle activity (12–16 Hz). All ANCOVA and regression models are arranged identically to our primary analyses in our main paper. All supplemental tables and figures present data from both Fz and Cz to facilitate comparisons.

Coupling Strength (MI) Between Nights

All SO Events. Presented in Table S1 are descriptive statistics of SO – σ MI in each channel, and results from repeated-measures ANCOVA testing for differences between nights. No significant main effects of study night were found on either channel.

SO+Spindle (SO(+)) and SO-Spindle (SO(-)) Events. Presented in Table S2 are descriptive statistics for the raw SO(+) and SO(-) events, and associated F1 ratios. Unsurprisingly, there were fewer

SO(+) events than SO(-) events, but the incidence of SO(+) events was systematically higher on Fz versus Cz, regarding both absolute count (t-range (24) = 4.589-4.939, all $p < .001$) and density (/30sec; t-range (24) = 4.747-5.156, all $p < .001$). However, the number of SO(+) and SO(-) events did not differ between nights on either channel (t-range (24) = -0.398–0.688, all $p > .498$). SO and spindle co-occurrence (via F1) was generally low, but still highly correlated across both nights (r-range = 0.619-0.689, all $p \leq 0.001$). Presented in Table S3 are descriptive statistics and results of between-night comparisons of SO(+) and SO(-) MI. No main effects of study night were found on either channel.

Raw Coupling Phase Between Nights

All SO Events. We next looked for effects of learning on the preferred SO – σ raw coupling phase (in radians, 0–360°) using circular statistics (Table S4). Rayleigh tests confirmed a unimodal circular distribution for measures from both channels (all ps $\leq .028$), however there were no differences in raw coupling phase between nights ($F_{W\text{-}W}$ (Fz) = 0.558, $p = .052$; $F_{W\text{-}W}$ (Cz) = 0.040, $p = .550$). Plots displaying phase-amplitude dynamics for these measures are shown in Figures S1. Slower sigma power on Fz tended to peak during the up-to-down SO transition phase, while faster sigma power on Cz was more tightly coupled across subjects to before or during the SO up-state.

SO+Spindle (SO(+)) and SO-Spindle (SO(-)) Events. Coupling phase distributions for each SO(+) and SO(-) condition is plotted in Figure S2, with circular statistics in Table S4. Rayleigh tests confirmed a unimodal circular distribution across both band-pair conditions from Fz during baseline (all ps $\leq .042$), and on the learning night (all ps $< .048$). On Cz, a unimodal circular distribution was found only for SO(-) – σ ($p = .013$) on the baseline night, however a unimodal distribution was found for both SO(+) and SO(-) measures on the learning night (all ps $< .035$). There were no differences in raw coupling phase between nights ($F_{W\text{-}W\ range} = <$ 0.001-0.657, all ps $> .069$).

Absolute Coupling Phase Distance from the Up-State (CP) Between Nights

All SO Events. Consistent with our main analysis on Fz, no main effects or interactions were found for differences in CP between nights on channel Cz (Table S5).

SO+Spindle (SO(+)) and SO-Spindle (SO(-)) Events. Presented in Table S6 are descriptive statistics for the CP measure for each SO(+) and SO(-) band-pair, and results from repeated-measures ANCOVA testing for differences between nights. No main effects or interactions were found for differences in CP between nights on Fz or Cz.

Coupling Strength (MI) and Relations with Overnight Memory Consolidation

All SO Events. As presented in Table S7, and consistent with our main analyses on Fz, relative change in MI between nights (rel_MI) on Cz was not significantly associated with overnight memory consolidation in this sample.

SO+Spindle (SO(+)) and SO-Spindle (SO(-)) Events. As presented in Table S7, a statistically significant association was found for SO(+) – σ rel_MI on Cz (F (3, 21) = 5.570, ΔR^2 = 0.269, p = .006, *B(SE)* = -6.022 (1.891), β = -.559), suggesting that a greater increase in SO(+) MI with faster spindle power after learning predicts worse memory consolidation.

Raw Coupling Phase and Relations with Overnight Memory Consolidation

All SO Events. Presented in Table S4 are SO – σ circular-linear correlations between SO – σ raw coupling phase on the learning night and word-pair overnight memory consolidation. No significant correlations were found on either (Fz or Cz) channel.

SO+Spindle (SO(+)) and SO-Spindle (SO(-)) Events. Table S4 also shows circular-linear correlations between raw coupling phase and word-pair memory consolidation, derived from SO(+) and SO(-) events on both channels. Only one trend-level correlation was found for SO(-) – σ raw coupling phase on Cz with memory consolidation (r = 0.49, p = .05). No other effects were observed.

Coupling Phase Distance from the Up-State (CP) and Relations with Memory Consolidation

All SO Events. As presented in Table S8 and Figure S3, and in contrast to our main paper, SO – σ rel_CP with fast spindle activity from Cz was not associated with memory consolidation in this sample.

SO+Spindle (SO(+)) and SO-Spindle (SO(-)) Events. Lastly, we examined relative change in CP derived from SO(+) and SO(-) events in predicting memory consolidation. As shown in Table S8, the addition of SO(-) – σ rel_CP yielded a statistically significant model (F (3, 21) = 4.985, ΔR^2 = 0.242, p =

.009; *B(SE)* = -0.098 (0.033), β = -.518), suggesting that a shift in coupling phase towards (vs. away from) the up-state predicted better memory, as in our main paper. No other associations were found on Fz or Cz.

Exploratory Interaction between MI and CP, and Relations with Memory Consolidation

All SO Events. An equivalent interaction model to the one presented in our main paper was repeated using data reflecting SO-coupling with fast spindle activity measured on Cz. The base interaction model did not yield a significant prediction of memory scores in this sample, and thus no follow-up analyses were performed (Table S9).

S.2. Examining CFC and Relations with Memory on Each Night Considered Separately

To further clarify our primary results from a combined N2+N3 sleep stage, we repeated our hierarchical regression analyses using MI and CP (all SO events) derived from each night individually. As shown in Table S10, MI was not predictive of memory consolidation in either channel on either night. By contrast, as shown in Table S11, CP closer to the up-state on Fz during the learning night predicted better memory consolidation (F (3, 21) = 4.809, ΔR^2 = 0.233, p = .011; *B(SE)* = -0.094 (0.033), β = -.631), whereas a similar effect was not observed on the initial/baseline night, or on either night from channel Cz.

S.3. Examining CFC and Learning/Memory in Stage N2 and N3 Considered Separately

Given that our focus was on data from a combined N2+N3 sleep stage, we repeated our primary CFC analyses (using all SO events) to examine between-night differences (MI: Table S12; CP: Table S13) and relations with memory (MI: Table S14; CP: Table S15) across stages N2 and N3 considered separately. There were no between-night differences in MI or CP in either stage across both channels. SO – σ raw coupling phase (Table S16) also did not differ between nights, with exception of CFC during N2 on channel Fz (*F(W-W) = 1.051, p* = .020, did not survive *p*-value correction); see Figure S4 (Panel A). Associations with memory were sparce. Change in MI (rel_MI) was negatively associated with memory consolidation during N2 on Fz (F (3, 20) = 3.663, ΔR^2 = 0.166, p = .030; *B(SE)* = -5.987 (2.643), β = -.414; Table S14); this result suggests that a larger increase in MI after learning predicted lower memory scores, however the significance of this finding did not survive our *p*-value correction. Raw coupling phase evidenced a circular-linear correlation with memory only during N3 on Cz (i.e., with fast spindle

activity; $r = 0.51$, $p = .039$, did not survive p-value correction; Table S16), which suggested a raw coupling phase peaking earlier in time before the up-state is associated with better memory, while a peak that occurs too long after the up-state is associated with worse memory. No other associations with memory were found among remaining MI, CP, or raw coupling phase variables when sleep stages were examined separately, including our exploratory moderation model between MI and CP (data not shown for parsimony).

S.4. Additional Control Analyses: PSD and Impact of Sleep Apnea

Power Spectral Density in Relation to Learning and Memory Consolidation

Presented in Table S17 are descriptive statistics of normalized PSD values from NREM sleep in each bandwidth (SO, sigma) and between-night comparisons. Presented in Table S18 are regression models like those above, with relative change between nights in PSD as a predictor of memory consolidation. There were no significant main effects of recording night on either channel for any PSD measure (F (1, 22)-range: 0.042–0.889; all ps > .356), and there were no significant associations found with word-pair memory consolidation.

Sleep Apnea Severity and Primary/Secondary Variables

The sample includes participants with a range of sleep apnea severity, with mild sleep apnea overall (M [SD] = 9.38 [7.87]). Of the whole sample, 32% had an AHI of 0–5/hr, 40% had an AHI of 5–15/hr, and 28% had an AHI of 15–29/hr. Nevertheless, a series of one-way ANOVAs found no significant differences between the means of these three sub-groups on any demographic, sleep/EEG parameter, memory, and CFC parameter. However, participants with an AHI > 15 events/hr evidenced greater sleep fragmentation on the baseline night than those with an AHI < 5 events/hr (25.18 vs. 20.07; $p = .032$).

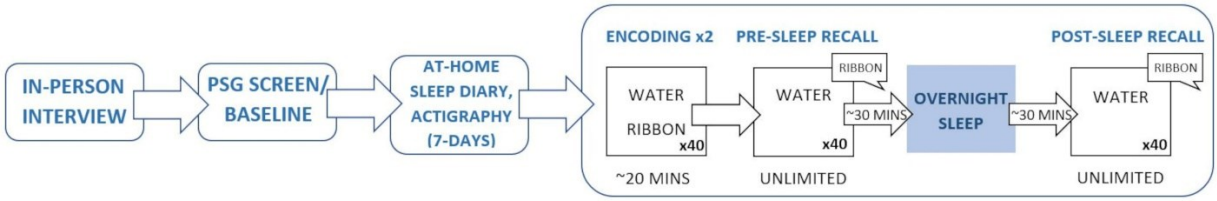

Figure 1. Schematic of the study design. Participants deemed eligible after the in-person interview underwent a first night of polysomnography (PSG) screening. If no major sleep disorder was detected (e.g., severe sleep apnea), participants returned at least 7 days later for a learning task night (word-pair associate's task). Participants completed daily sleep diary entries and were monitored by wrist actigraphy between the two recording visits. In the learning task, participants were shown a list of 40 word-pairs, with two list presentations during encoding. Encoding was followed by a pre-sleep (PM; short-delay) cued recall test, where the first word was displayed and participants had to recall the associated word. Verbal responses were recorded by a research assistant. The next morning after overnight sleep, participants completed a post-sleep (AM; long-delay) cued recall test.

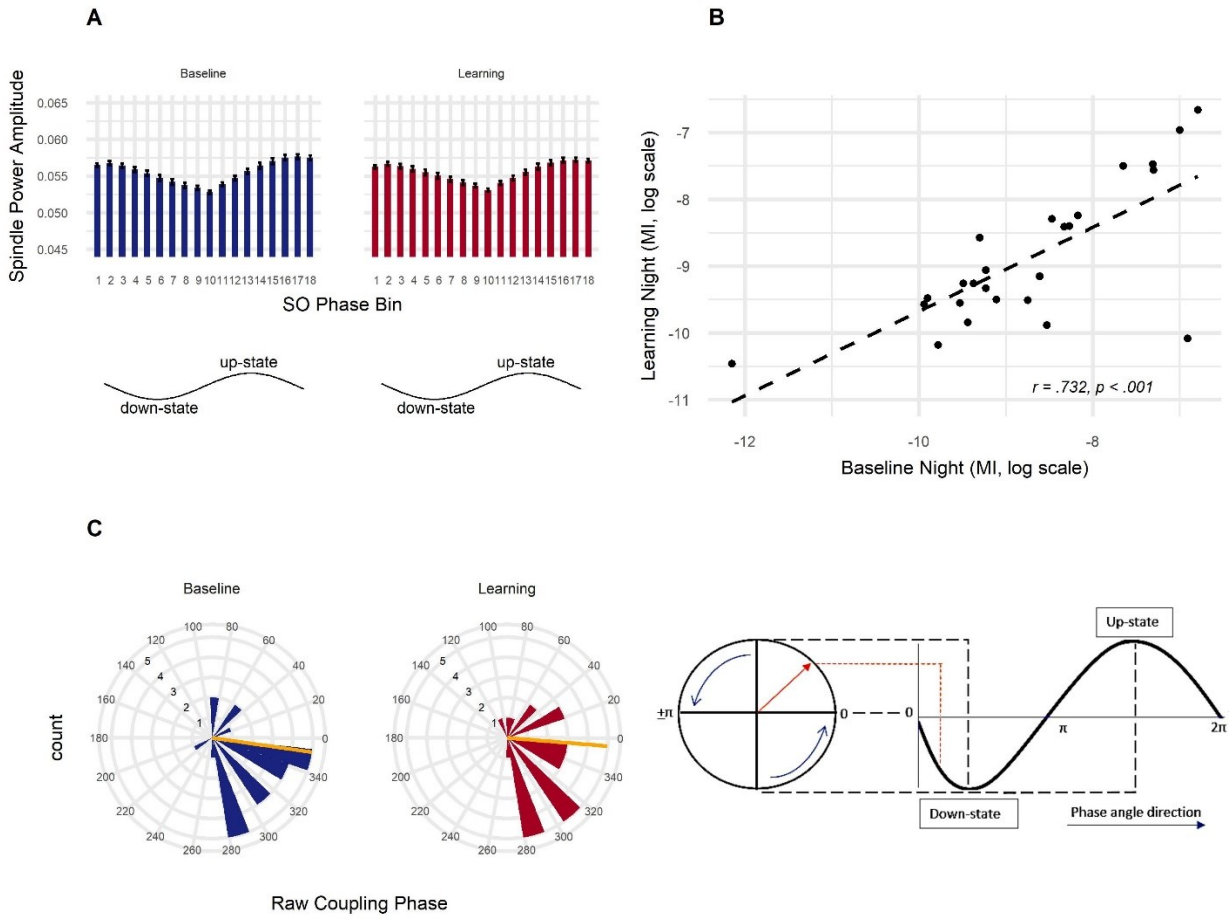

Figure 2. Schematic representation of coupling dynamics. **A**, Phase-amplitude histograms for Night 1/baseline (blue) and Night 2/learning (red) conditions. Each vertical bar reflects the sigma power mean amplitude (μV; y-axis) across each of the 18 x 20-degree phase bins (x-axis). Error bars are for the standard error of the mean. Plotted below the histogram is a reference for the oscillation phase across the 18 bins; the hyperpolarizing SO down-state is pointing down, and is followed by the depolarizing up-state, pointing up. Overall, slower sigma power amplitude peaked more in the up-to-down-state transition and was at its lowest shortly before the up-state. **B**, Scatterplot displaying correlation for SO – σ Modulation Index (MI) between the baseline night (x-axis) and learning night (y-axis). The dashed line indicates equality from one night to the next. Correlation analysis suggests that SO – σ MI might be a stable, individual (trait-like) property in older adults. **C**, Preferred (raw) coupling phase polar plots for Night 1/baseline (blue) and Night 2/learning (red). Each coloured bar represents the number of

participants with the same overall coupling phase. The count scale (pointing to 130 deg on the circle) is reflected by the concentric rings extending from the center of each circular figure. The orange line reflects the average coupling phase of the group on each night. The depolarizing SO up-state corresponds to 270 deg on the circle (6:00 position) and hyperpolarizing down-state corresponds to 90 deg on the circle (12:00 position), with the phase-angle direction moving counter-clockwise. Consistent with (**A**), slower frontal spindle power tended to peak after the up-state phase. Next to (**C**) is a graphical legend of SO phase angle and its relationship with the polar plots, with an example phase in orange (adapted from Ong et al., 2016).

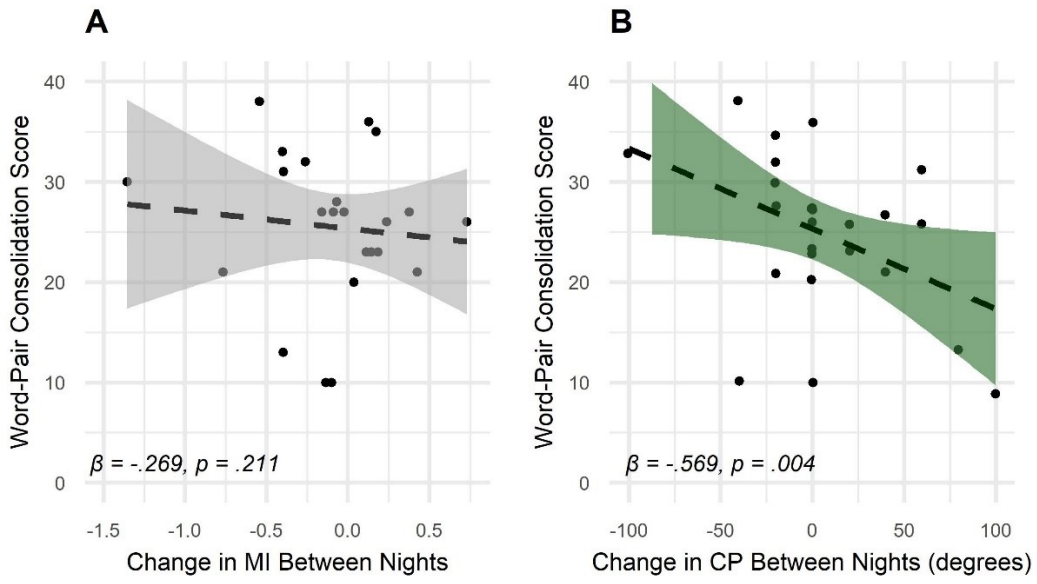

Figure 3. **A**, Scatterplot displaying association of word-pair memory consolidation score (on y-axis) with relative change in SO – σ MI between nights from Fz (rel_MI; x-axis). Values of rel_MI above zero reflect greater coupling strength on the learning night. **B**, Scatterplot displaying association of word-pair memory consolidation score (on y-axis) with relative change in SO – σ CP between nights from Fz (rel_CP; x-axis). Negative associations (and negative beta value) correspond with the data structure of negative values on this relative CP variable reflecting a shift closer to (vs. further from) the SO up-state after learning compared to baseline; a greater shift towards the up-state after learning predicted better memory consolidation. Standardized coefficient and *p*-value on each plot is from hierarchical regression models examining rel_MI or rel_CP in predicting word-pair memory performance, controlling for age and sleep apnea severity.

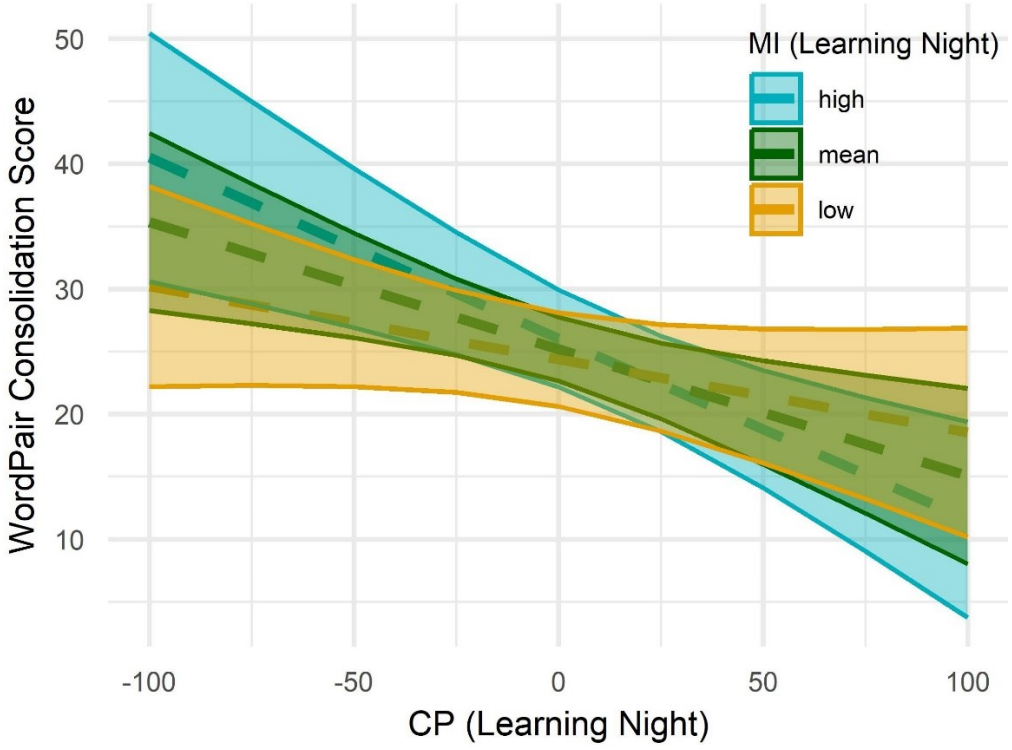

Figure 4. Simple slopes reflecting the association between mean-centered CP on Fz (learning night only; x-axis) in predicting word-pair task memory consolidation scores (y-axis) at high, average, and low levels of MI (learning night only). The negative slope reflects the data structure of lower (more negative) CP values signifying a coupling phase distance closer to the SO up-state peak. Coloured ribbons reflect 95% confidence intervals. CP closer to the up-state peak evidenced a stronger predictive association with better memory consolidation when MI values were adjusted higher by 1 SD-unit (β = -.978, p = .001; blue dotted line) compared to MI values adjusted lower by 1 SD-unit (β = -.381, p = .120; orange dotted line). The overall model was statistically significant (F(5, 19) = 4.399, ΔR^2 = 0.362, p = .008). Taken together, relations between SO – σ coupling phase closer to the up-state and better memory consolidation may be enhanced when coupling strength is higher and blunted when coupling strength is lower.

Table 1

Demographics and Screening. N = 25.

	M	SD	Min-Max
Demographics			
Age	69.12	5.53	58-78
Sex (% Female)	64%	-	-
Language (% French)	80%	-	-
Handedness (% Right)	80%	-	-
Height (in)	63.93	4.49	50.60-70.55
Weight (lbs)	157.49	33.36	94.40-217.80
BMI (kg/m^2)	26.87	3.77	19.94-31.75
Education (yrs)	16.78	3.50	12-26
Assessments/Questionnaires			
MMSE	28.56	0.92	27-30
MoCA	27.84	1.80	24-30
Insomnia Severity Index	3.28	2.75	0-9
PSQI Total	2.72	1.86	1-7
PSQI Sleep Quality	0.36	0.49	0-1
Epworth Sleepiness Scale	5.52	3.53	0-11
MEQ	64.84	7.20	51-80
STOP-Bang	2.32	1.31	1-5
Geriatric Anxiety Inventory	0.68	1.22	0-4
Geriatric Depression Scale	2.32	2.39	0-9

Note: MMSE, Mini Mental State Exam; *MoCA*, Montreal Cognitive Assessment; *PSQI*, Pittsburgh Sleep Quality Index; PSQI Sleep Quality, closer to zero = better sleep quality; MEQ, Morningness-Eveningness Questionnaire. *M,* mean; *SD,* standard deviation.

Table 2

Sleep architecture of PSG (Night 1, Baseline) and EEG (Night 2, Learning) recording visits, and between-night differences. N = 25.

	Baseline ***M (SD)*** **[Min-Max]**	**Learning** ***M*** **(SD)** **[Min-Max]**	***t*** **(df=24)**	***p***
Total Sleep Time (mins)	391.72 (62.03) [280.50-512]	403.00 (52.73) [308.50-488.50]	-1.425	.167
Sleep Efficiency (%)	83.26 (7.03) [70.12-94.88]	85.71 (7.27) [72.32-96.42]	-2.472	.021
Sleep Onset Latency (mins)	10.49 (10.98) [0.75-56.50]	7.18 (6.86) [0.50-26.00]	1.613	.120
WASO (mins)	61.74 (32.23) [16-135]	53.78 (29.89) [5.50-114]	1.484	.151
N1 (% of sleep time)	16.48 (5.95) [6.21-29.71]	15.39 (5.54) [6.76-28.03]	0.970	.342
N2 (% of sleep time)	52.35 (8.19) [38.50-65.33]	52.42 (6.17) [34.21-61.43]	-0.043	.966
N3 (% of sleep time)	12.81 (7.20) [4.08-28.77]	13.18 (4.92) [4.98-23.20]	-0.292	.772
REM (% of sleep time)	18.36 (4.31) [10.79-30.26]	19.01 (5.66) [8.59-29.89]	-0.521	.607
Apnea-Hypopnea Index (/hr)	9.38 (7.87) [0.80-28.30]	-	-	-
Sleep Fragmentation Index (#/hr)	11.57 (2.38) [7.98-17.09]	11.76 (3.56) [6.63-22.93]	-0.375	.711
Stage Switch Index (#/hr)	22.81(3.97) [17.13-29.48]	23.41 (5.41) [15.35-40.35]	-0.760	.455

Note. N1, non-rapid-eye-movement (NREM) stage 1; N2, NREM stage 2; N3, NREM stage 3; REM, rapid-eye-movement sleep; WASO, wake after sleep onset. *M*, mean; *SD*, standard deviation. Mins, minutes; hr, hour. Negative *t*-values indicate a larger value on Learning (Night 2) visit.

Table 3

Detected Slow Oscillations and Sleep Spindles on Fz across study nights. N = 25.

	Baseline [*M* (*SD*)]	**Learning [*M* (*SD*)]**	***t* (df=24)**	***p***
Slow Oscillations (SO)				
Density (/30s)	3.09 (0.67)	3.04 (0.61)	0.389	.701
Mean Duration (sec)	1.38 (0.05)	1.39 (0.05)	-1.999	.057
Peak-to-Peak Amplitude (μV)	117.45 (32.37)	114.68 (32.20)	1.426	.167
Power (μV^2)	613.73 (414.90)	603.35 (409.50)	0.431	.670
Peak Energy Freq (Hz)	0.69 (0.03)	0.68 (0.03)	1.803	.084
Sleep Spindles				
Density (/30s)	1.75 (0.24)	1.78 (0.19)	-1.032	.312
Mean Duration (sec)	0.78 (0.05)	0.78 (0.04)	1.388	.178
Peak-to-Peak Amplitude (μV)	88.63 (23.13)	84.44 (20.57)	2.712	.012
Power (μV^2)	59.52 (43.51)	51.22 (29.00)	2.045	.052
Peak Energy Freq (Hz)	10.89 (0.39)	10.85 (0.40)	1.544	.136

Note. *M*, mean; SD, standard deviation. Freq, frequency. sec, seconds; μV; microvolts; Hz, Hertz. Negative *t*-values indicate a larger value on Learning (Night 2) visit. Pearson's correlations revealed highly stable values for each measure from the first to second overnight recording (SOs: all $r \geq 0.614$, all $p \leq .001$; Spindles: all $r \geq 0.814$, all $p < .001$).

Table 4

Descriptive statistics and between-night comparison of SO-sigma MI and CP from Fz. N = 25.

	Baseline ***M* (*SD*), [*Med*]**	**Learning** ***M* (*SD*), [*Med*]**	**Type III SS**	**df**	**Mean Square**	***F***	***p***	**Partial η^2**
Coupling Strength (MI)								
SO – σ MI, Night (1 vs. 2)	-8.74 (1.21), [-8.75]	-8.89 (1.04), [-9.26]	0.898	1	0.898	3.252	.085	.129
Night X Age			0.507	1	0.507	1.838	.189	.077
Night X Log_AHI			1.643	1	4.643	5.951	.023	.213
Error (Night)			6.074	22	0.276			
Absolute Coupling Phase Distance from Up-State (CP)								
SO – σ CP, Night (1 vs. 2)	68.80 (49.36), [60.00]	74.40 (53.08), [60.00]	3105.376	1	3105.376	3.784	.065	.147
Night X Age			2902.033	1	2902.033	3.537	.073	.138
Night X Log_AHI			11.685	1	11.685	0.014	.906	.011
Error (Night)			18052.784	22	820.581			

Note. SO, slow oscillation (0.5–1.25 Hz); σ, sigma (fixed at 9–13 Hz). MI, Modulation Index. CP, absolute coupling phase distance from the SO up-state. *M*, mean; SD, standard deviation, med, median. *F*-statistic, *p*-value, and Partial η^2 are for repeated-measures ANCOVA with Night (1/baseline vs. 2/learning) as the repeated-measures factor. Age and apnea-hypopnea index (log-transformed; measured on Night 1) were included as covariates. Pearson's correlations revealed highly stable values for each measure from the first to second overnight recording (MI: $r = 0.732$, $p < .001$; CP: $r = 0.669$, $p < .001$), but no significant relationship between MI and CP on either night (r-range: -0.136–0.140, all $p > .504$).

Table 5

Hierarchical regression to predict word-pair Consolidation Score by SO-sigma rel_MI and rel_CP from Fz. N = 25.

Model	*F* (df)	*p*	ΔR^2	*B* (*SE*)	*β*	$p_{(\beta)}$
Coupling Strength (MI)						
1. Age, AHI [a]	2.682 (2, 20)	.093	0.212			
2. SO – σ rel_MI [a]	2.407 (3, 19)	.099	0.064	-4.650 (3.594)	-.269	.211
Absolute Coupling Phase Distance from Up-State (CP)						
1. Age, AHI	2.322 (2, 22)	.122	0.174			
2. SO – σ rel_CP	**5.792 (3, 21)**	**.005**	**0.278**	**-0.108 (0.033)**	**-.569**	**.004**

Note. SO (0.5–1.25 Hz); σ, sigma (fixed at 9–13 Hz). rel_MI, change in Modulation Index between nights. rel_CP, change in absolute coupling phase distance from the SO up-state between nights. *F*-statistic, *p*-value, ΔR^2, *B (SE), β,* and *p*(*β*) are from hierarchical regression models with the coupling measure of interest as the independent variable predicting word-pair consolidation in Model 2. Age and apnea-hypopnea index (log-transformed; measured on Night 1) were entered in Model 1. *p*(*β*) is *p*-value associated with the standardized regression coefficient for the independent variable, controlling for other model predictors. Values in **bold** denote results that reached or surpassed Bonferroni-adjusted *p*-value (.013). *B*, unstandardized coefficient. *B*, standardized coefficient; ΔR^2, change in proportion of explained variance; SE, standard error. [a], *n* = 23, 2 participants removed as outliers prior to analysis with rel_MI on Fz.

Table 6

Hierarchical regression to predict word-pair consolidation score by SO-sigma MI and CP interaction from Fz on the learning night. N = 25.

	***F* (df)**	***p***	**ΔR^2**	***B* (*SE*)**	***β***	***p*(*β*)**
Model 2						
SO – σ (base)						
MI [a]	-		-	-0.833 (1.354)	-.109	.546
CP [a]	-		-	**-0.102 (0.031)**	**-.680**	**.004**
MIxCP	**4.399 (5, 19)**	**.008**	**0.362**	**-0.043 (0.019)**	**-.384**	**.033**
SO – σ						
MI (Lower) [b]	-		-	-0.834 (1.354)	-.109	.545
CP [a]	-		-	-0.057 (0.035)	-.381	.120
MI(Low)xCP	-		-	**-0.043 (0.019)**	**-.461**	**.033**
SO – σ						
MI (Higher) [c]	-		-	-0.834 (1.354)	-.109	.545
CP [a]	-		-	**-0.146 (0.039)**	**-.978**	**.001**
MI(High)xCP	-		-	**-0.043 (0.019)**	**-.512**	**.033**

Note. SO (0.5–1.25 Hz); σ, sigma (fixed at 9–13 Hz for Fz). MI, Modulation Index; CP, absolute coupling phase distance from the SO up-state. *F*-statistic, *p*-value, ΔR^2, *B (SE), β,* and *p*(*β*) are from hierarchical regression models to predict word-pair consolidation (Model 2) with centered MI and CP values included alongside a product term reflecting their interaction. Age and apnea-hypopnea index (log-transformed; measured on Night 1) were entered in Model 1. *F*-statistic and ΔR^2 is presented only for the final model with interaction term. ΔR^2, change in proportion of explained variance; SE, standard error. *B*, unstandardized coefficient. *β*, standardized coefficient. *p*(*β*) is *p*-value associated with the standardized regression coefficient for the independent variable, controlling for other model predictors. Values in **bold** denote results that surpassed the conventional critical *p*-value (< .05). "(base)" refers to the baseline interaction model, containing two mean-centered predictors and their product as an interaction term; models in the two subsequent rows present follow-up analyses to examine moderating effects of MI when a significant interaction was found in the base model (See also Figure 4). Note that regression coefficients for the moderator variable (MI) remain unchanged across each interaction model, whereas the unstandardized and standardized coefficients for CP are recalculated for each model; only the standardized coefficient for the interaction term changes across models. [a], mean-centered main-effect predictor; [b], mean-centered moderator values adjusted down by 1 SD-unit below the mean (i.e., lower MI); [c], main-centered moderator values adjusted up by 1 SD-unit above the mean (i.e., higher MI).

SUPPLEMENTAL MATERIAL – STUDY 1

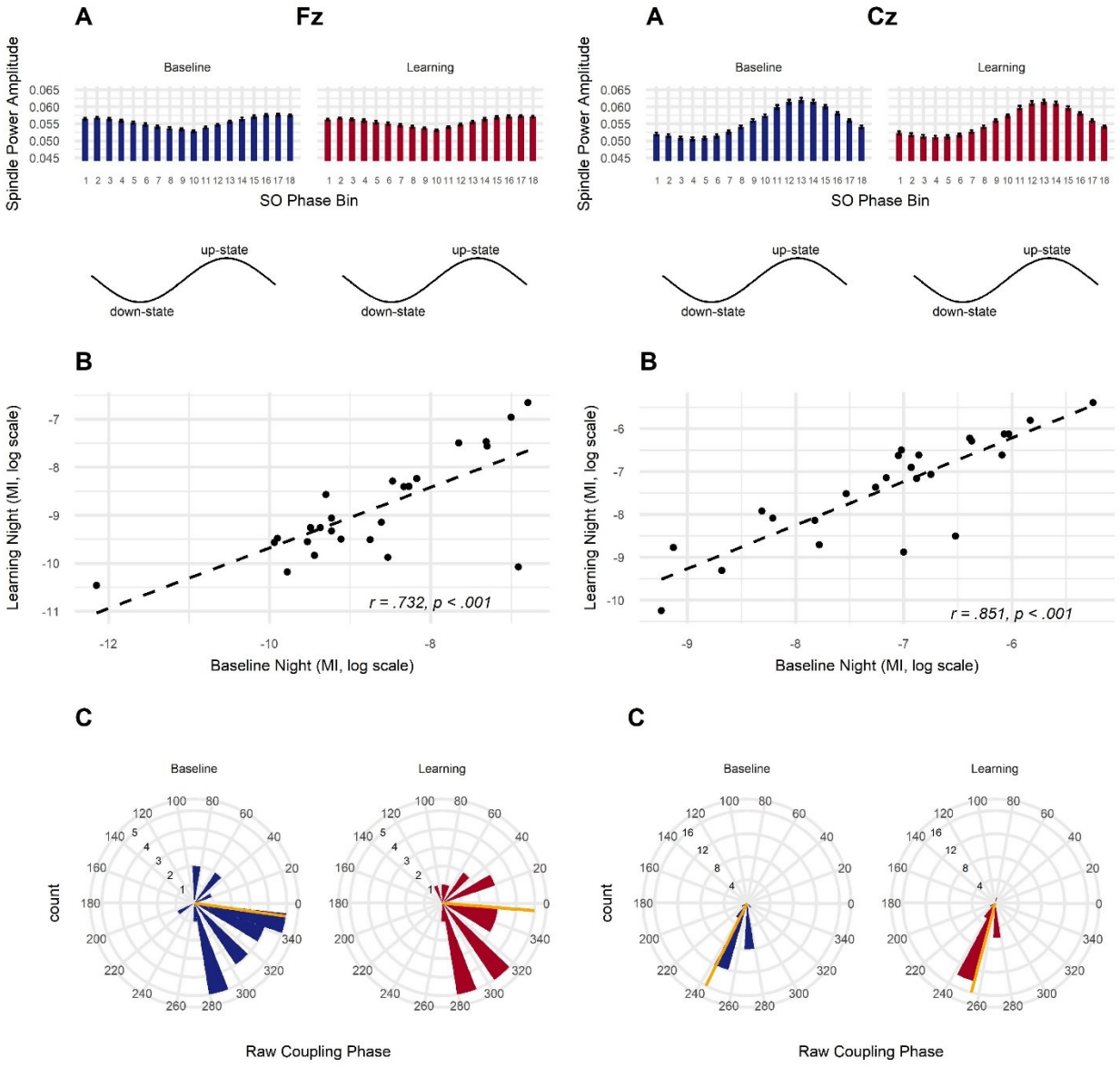

Figure S1. Schematic representation of coupling dynamics. On the left panel is data from Fz (9–13 Hz), and on the right panel is data from Cz (12–16 Hz). **A** (**both panels**), Phase-amplitude histograms for Night 1/baseline (blue) and Night 2/learning (red) conditions. Each vertical bar reflects the sigma power mean amplitude (μV; y-axis) across each of the 18 x 20-degree phase bins (x-axis). Error bars are for the standard error of the mean. Plotted below each histogram is a reference for the oscillation phase across the 18 bins. Compared to Fz, where sigma amplitude peaked across the up-to-down-state transition, peak sigma

amplitude on Cz was more clearly defined near the SO up-state. **B** (**both panels**), Scatterplot displaying correlation for SO – σ Modulation Index (MI) between the baseline night (x-axis) and learning night (y-axis). The dashed line indicates equality from one night to the next. Equivalently strong positive correlations were found for SO – σ MI in both channels (r range = 0.732-0.851, both ps < .001), further suggesting that SO – σ MI may be a stable, trait-like property in both slow-frontal and fast-central sigma power contexts. **C** (**both panels**), Preferred raw coupling phase polar plots for Night 1/baseline (blue) and Night 2/learning (red). Each coloured bar represents the number of participants with the same overall coupling phase. The count scale (pointing to 130 deg on the circle) is reflected by the concentric rings extending from the center of each circular figure. The orange line reflects the average coupling phase of the group on each night. The SO up-state corresponds to 270 deg on the circle (6:00 position) and the down-state corresponds to 90 deg (12:00 position), with the phase-angle direction moving counter-clockwise. See Figure 2 for a legend to help interpret circular (polar) plots. Consistent with (**A**), the peak of slow frontal spindle power shows more inter-subject variability in coupling phase relative to fast central spindle power, which was more tightly clustered before or during the SO up-state.

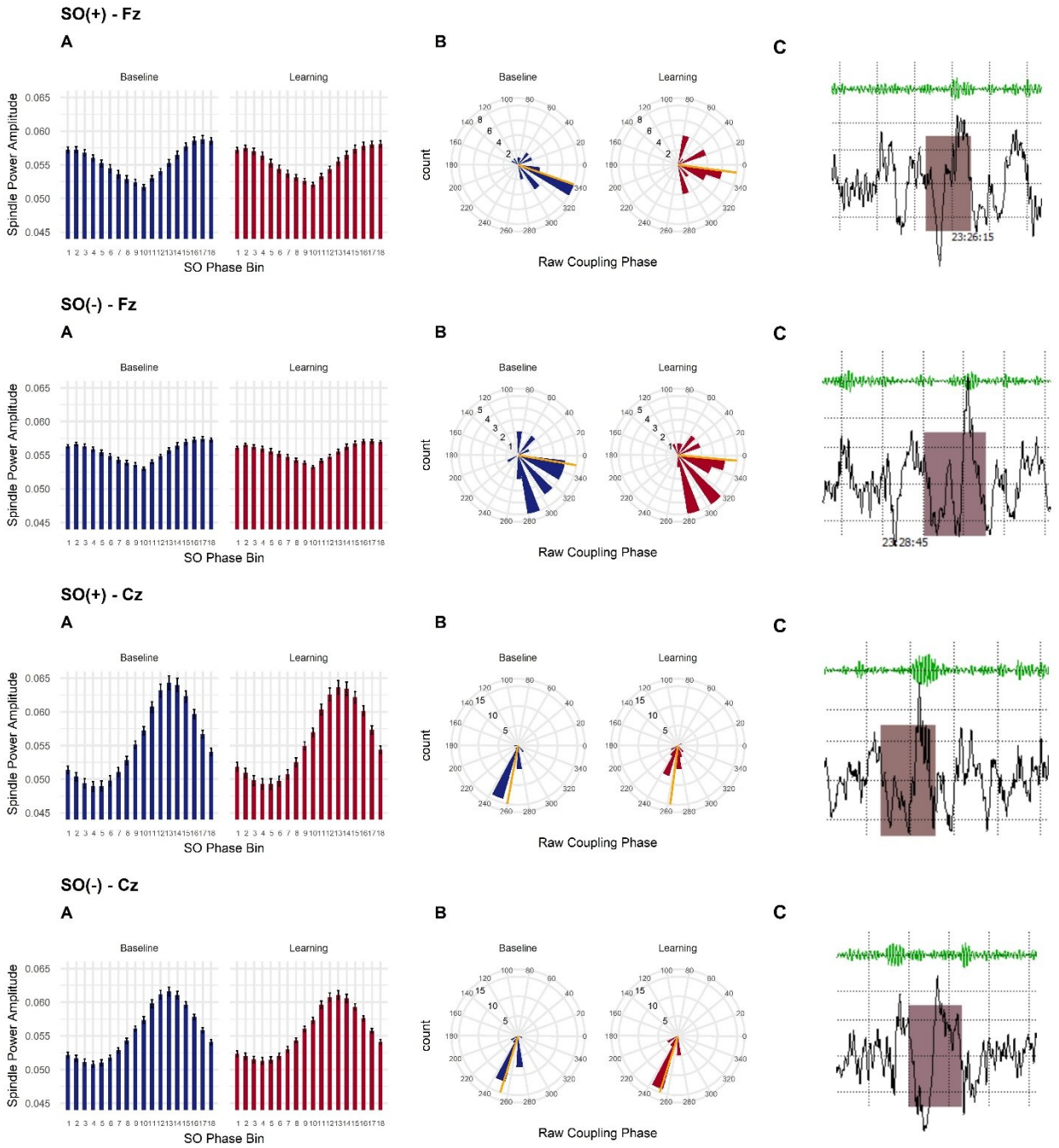

Figure S2. Schematic representation of coupling dynamics on subgroupings of SO-spindle complexes and isolated SO events. The top two rows contain data from Fz (9–13 Hz), and the bottom two rows contain data from Cz (12–16 Hz). The first row and third row both display data from SO(+) – σ, reflecting SO events joined with a detected spindle; the second row and fourth row both display data from SO(-) – σ, reflecting isolated SO events not joined with a spindle. **A** (**all panels**), Phase-amplitude histograms for

Night 1/baseline (blue) and Night 2/learning (red) conditions, following the same conventions as in previous figures. Overall, and like analyses with all SO events, peak sigma power amplitude is more clearly defined near the SO up-state on Cz, whereas amplitude increases are less well defined on Fz, with a peak during the up-to-down-state transition. Amplitude modulations were larger on SO(+) relative to SO(-) events in both channels. Similarly strong positive (across-night) correlations were found for MI in both channels and band-pair (SO(+) and SO(-)) conditions, but with smaller correlations on Fz (r range = 0.642-0.679, all $p <$ .001) relative to Cz measures (r range = 0.798-0.840, all $p <$ .001). **B** (**all panels**), Preferred (raw) coupling phase polar plots for Night 1/baseline (blue) and Night 2/learning (red), following the same conventions as in previous figures. Overall, the peak of slower frontal spindle power shows more inter-subject variability relative to coupling phase with faster central spindle power. **C** (**all panels**), Example segment of raw data from one participant on the learning night, showing a detected slow oscillation that overlapped with a detected sleep spindle (SO-spindle complex; first row and third row) and a detected slow oscillation without a detected spindle that met our overlap criteria (isolated SO events; second row and fourth row). The green-coloured trace above the detected oscillation in each image reflects the same EEG channel filtered between 9–16 Hz, and showing increases in sigma activity/power that accompany the SO.

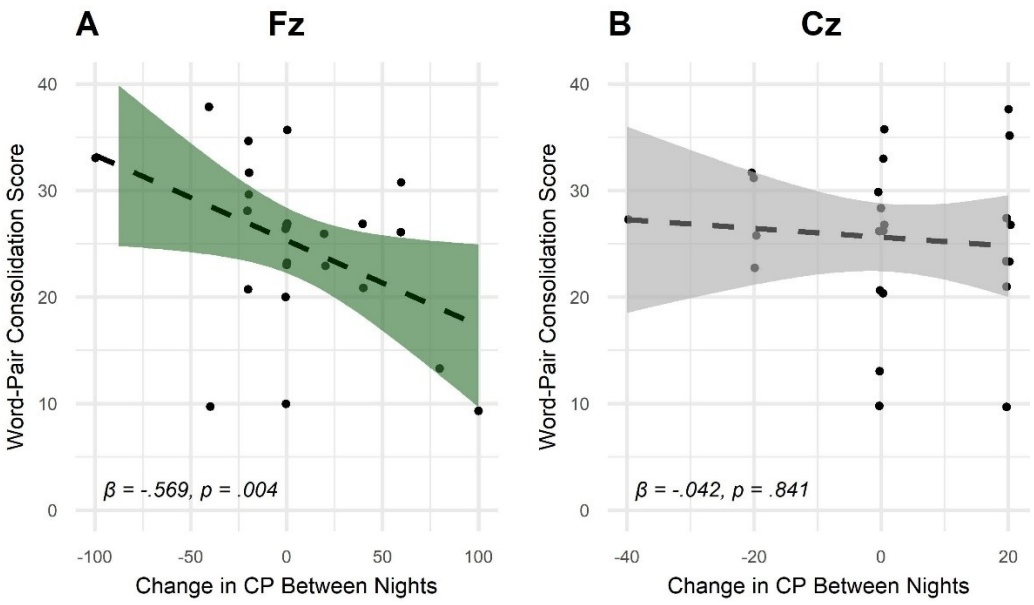

Figure S3. Scatterplots displaying association of word-pair memory consolidation score (on y-axis) with SO – σ relative CP (rel_CP, change in distance from the SO up-state during learning night minus baseline night, measured in degrees; x-axis). On the left half is rel_CP data from Fz (9–13 Hz), and on the right is data from Cz (12–16 Hz). Standardized coefficients and *p*-values are from hierarchical regression models examining the rel_CP variable in predicting memory performance, controlling for age and sleep apnea severity. Negative associations (and negative beta value) correspond with the data structure of negative values on this rel_CP variable reflecting a shift closer to (vs. further from) the SO up-state after learning (vs. baseline): a shift in absolute coupling phase closer to (vs. further from) the up-state after learning is associated with better memory performance, but only in the context of slow (frontal) spindle power.

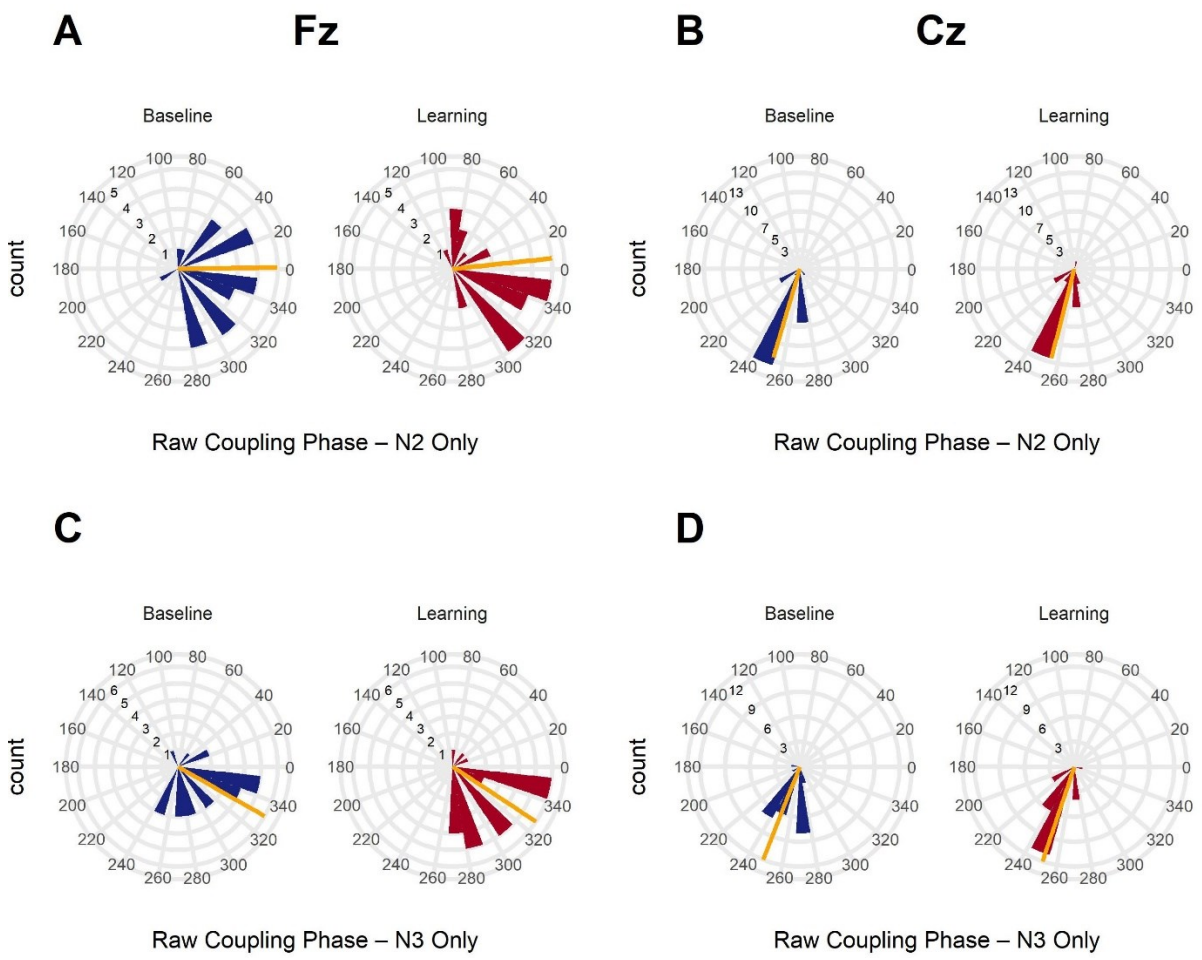

Figure S4. Preferred SO – σ coupling phase polar plots (all SO events) from Night 1/baseline (blue) and Night 2/learning (red) conditions, during stage N2 (**A** (Fz) and **B** (Cz)) and stage N3 (**C** (Fz) and **D** (Cz)) considered separately. Polar plots share the same conventions as in previous figures. As with analyses from N2+N3 sleep stages, the peak of slow frontal spindle power shows more inter-subject variability relative to coupling phase with fast central spindle power. Coupling phase with slower (Fz) spindle power shows a clustering that leans closer to the SO up-state during stage N3 relative to N2, whereas coupling phase with faster (Cz) spindle power was more consistent between stages N2 and N3.

Table S1

Between-night comparison of SO-sigma MI from Fz and Cz, from all SO events. N = 25.

	Baseline MI (*M* (*SD*), [*Med*])	**Learning MI (*M* (*SD*), [*Med*])**	**Type III SS**	**df**	**Mean Square**	***F***	***p***	**Partial η^2**
Channel Fz								
SO – σ MI Night (1 vs. 2)	-8.74 (1.21), [-8.75]	-8.89 (1.04), [-9.26]	0.898	1	0.898	3.252	.085	.129
Night X Age			0.507	1	0.507	1.838	.189	.077
Night X Log_AHI			1.643	1	4.643	5.951	.023	.213
Error (Night)			6.074	22	0.276			
Channel Cz								
SO – σ MI Night (1 vs. 2)	-7.13 (1.02), [-7.00]	-7.37 (1.22), [-7.15]	0.290	1	0.290	1.584	.221	.067
Night X Age			0.119	1	0.119	0.646	.430	.029
Night X Log_AHI			0.710	1	0.710	3.869	.062	.150
Error (Night)			4.036	22	0.183			

Note. SO, slow oscillation (0.5–1.25 Hz); σ, sigma, fixed bandwidth (9–13 Hz for Fz, 12–16 Hz for Cz). MI, Modulation Index. *M*, Mean; *SD,* Standard Deviation; *Med,* Median. *F*-statistic, *p*-value, and Partial η^2 are for repeated-measures ANCOVA with Night (1/baseline vs. 2/learning) as the repeated-measures factor. Age and apnea-hypopnea index (log-transformed; measured on Night 1) were included as covariates. Pearson's correlations revealed highly stable values from the first to second overnight recording for each measure on Fz ($r = 0.732$, $p < .001$) and on Cz ($r = 0.851$, $p < .001$).

Table S2

Descriptive counts and detection scores for sub-groups of overlapping SO-spindle events and isolated SO events across study nights and in channel Fz and Cz. N = 25.

	Slow Oscillation Sub-Groups							
	Count (Baseline) *M* (*SD*), [Min-Max]	**Count (Learning) *M* (*SD*), [Min-Max]**	***t* (24)**	***p***	**F1 Ratio (Baseline) *M* (*SD*), [Min-Max]**	**F1 Ratio (Learning) *M* (*SD*), [Min-Max]**	***t* (24)**	***p***
Channel Fz								
SO + Spindle	241.84 (86.35), [79-391]	232.28 (69.70), [122-394]	0.668	.498	0.19 (0.04), [0.11-0.29]	0.18 (0.04), [0.12-0.25]	1.473	.154
SO – Spindle	1349.20 (423.70), [437-2077]	1371.84 (369.58), [595-2344]	-0.398	.694		-		
Channel Cz								
SO + Spindle	190.84 (71.21), [61-378]	183.96 (56.70), [64-303]	0.646	.524	0.16 (0.03), [0.09-0.23]	0.15 (0.03), [0.08-0.21]	1.440	.163
SO – Spindle	1275.64 (402.03), [495-1929]	1297.20 (367.77), [601-2187]	-0.372	.713		-		

Note. *M*, mean; SD, standard deviation. SO + Spindle reflects SO events that are joined in time with a detected sleep spindle (minimum 25% overlap between events), and SO – Spindle reflects SO events not joined with a sleep spindle. F1 Ratio reflects the accuracy of detecting overlapping SO and spindle events and distinguishing these from isolated SO events without an overlapping spindle; F1 is calculated as the harmonic mean of scores reflecting precision (ratio of true positive hits:[true positives + false positives]) and recall (ratio of true positives:[true positives + false negatives]). In this context, an F1 score of 1 indicates that every SO overlapped with a spindle, and likewise every spindle overlapped with a SO. Negative *t*-values indicate a larger value on Learning (Night 2) visit. Pearson's correlations revealed highly stable values for each measure of absolute count from the first to second overnight recording (*r*-range: 0.622-0.751, all $p \leq .001$), and of F1 scores for SO(+) measures between nights (*r*-range: 0.619-0.689, all $p \leq 0.001$).

Table S3

Between-night comparison of SO-sigma MI on SO events joined with a spindle (SO(+)) or not joined by a detected spindle (SO(-)) from Fz and Cz. N = 25.

	Baseline MI (*M* (*SD*), [*Med*])	**Learning MI (*M* (*SD*), [*Med*])**	**Type III SS**	**df**	**Mean Square**	***F***	***p***	**Partial η^2**
Channel Fz								
SO(+) – σ MI Night (1 vs. 2)	-7.84 (0.93), [-7.98]	-8.07 (1.06), [-8.18]	0.490	1	0.490	1.580	.222	.067
Night X Age			0.200	1	0.200	0.647	.430	.029
Night X Log_AHI			1.518	1	1.518	4.899	.038	.182
Error (Night)			6.818	22	0.310			
SO(-) – σ MI Night (1 vs. 2)	-8.90 (1.21), [-8.80]	-9.02 (1.01), [-9.28]	0.940	1	0.940	2.682	.116	.109
Night X Age			0.564	1	0.564	1.611	.218	.068
Night X Log_AHI			1.485	1	1.485	4.239	.052	.162
Error (Night)			7.708	22	0.350			
Channel Cz								
SO(+) – σ MI Night (1 vs. 2)	-6.58 (1.22), [-6.28]	-6.53 (1.00), [-6.44]	0.089	1	0.089	0.350	.560	.016
Night X Age			0.029	1	0.029	0.114	.739	.005
Night X Log_AHI			0.845	1	0.845	3.321	.082	.131
Error (Night)			5.599	22	0.255			
SO(-) – σ MI Night (1 vs. 2)	-7.22 (0.97), [-7.10]	-7.51 (1.27), [-7.22]	0.309	1	0.309	1.372	.254	.059
Night X Age			0.123	1	0.123	0.547	.467	.024
Night X Log_AHI			0.670	1	0.670	2.975	.099	.119
Error (Night)			4.951	22	0.225			

Note. SO (0.5–1.25 Hz); σ, sigma, fixed bandwidth (9–13 Hz for Fz, 12–16 Hz for Cz). MI, Modulation Index. SO(+) – σ reflects SO events joined with a detected spindle; SO(-) – σ reflects SO events not joined with a detected spindle. *M*, Mean; *SD,* Standard Deviation; *Med,* Median.

F-statistic, *p*-value, and Partial η^2 are for repeated-measures ANCOVA for MI with Night (1/baseline vs. 2/learning) as the repeated-measures factor. Age and apnea-hypopnea index (log-transformed; measured on Night 1) were included as covariates. Pearson's correlations revealed modestly stable values from the first to second overnight recording for each measure on Fz (SO(+): $r = 0.642$, $p = .001$; SO(-): $r = 0.679$, $p < .001$) and stronger correlations on Cz (SO(+): $r = 0.798$, $p < .001$; SO(-): $r = 0.840$, $p < .001$.

Table S4

Circular statistics of SO-sigma raw coupling phase between experimental nights on Fz and Cz, from all SO events, co-occurring SO-spindle events (SO(+)), and SOs not joined by a detected spindle (SO(-)). N = 25.

	Baseline				Learning				Between Nights		Circular-Linear Correlation with Memory Consolidation	
	Angle	**R**	**Z**	$p_{(Z)}$	**Angle**	**R**	**Z**	$p_{(Z)}$	$F_{(W\text{-}W)}$	$p_{(W\text{-}W)}$	***r***	***p***
Channel Fz												
SO – σ	4.57	0.02	52.10	.028	4.03	0.02	45.87	.020	0.558	.052	0.27	0.41
SO(+) – σ	4.27	0.04	18.98	.040	3.94	0.03	14.56	.048	< 0.001	.992	0.07	0.95
SO(-) – σ	4.52	0.02	36.83	.042	4.25	0.02	33.58	.013	0.657	.069	0.30	0.32
Channel Cz												
SO – σ	4.45	0.05	146.08	.014	4.25	0.05	132.83	.010	0.040	.550	0.44	0.09
SO(+) – σ	4.51	0.07	33.07	.071	4.36	0.07	30.69	.005	-	-	0.35	0.22
SO(-) – σ	4.45	0.05	115.64	.013	4.31	0.05	105.30	.035	0.018	.704	0.49	0.05

Note. SO, slow oscillation (0.5–1.25 Hz); σ, sigma, fixed bandwidth (9–13 Hz for Fz, 12–16 Hz for Cz). SO(+) – σ reflects SO events joined with a detected spindle; SO(-) – σ reflects SO events not joined with a detected spindle. *Angle* and *R* are the group average direction and length of the resultant vector of the coupling phase distribution, respectively. *Z*-statistic and associated *p*-value are the group average for the Rayleigh test for non-uniformity of a circular distribution. Between-night differences in raw coupling phase was examined using a Watson-Williams test for unequal means in circular distributions, with associated *F*-statistic and *p*-value. Watson-Williams test was only performed when the Rayleigh test showed significant coupling on both nights at $p < .05$. There were no differences in coupling phase (raw score) between nights. Circular-linear correlations between raw coupling phase and memory consolidation is specific to coupling phase from the learning-task night only.

Table S5

Between-night comparison of SO-sigma CP on all SO events from Fz and Cz. N = 25.

	Baseline CP (*M* (*SD*), [*Med*]	**Learning CP (*M* (*SD*), [*Med*]**	**Type III SS**	**df**	**Mean Square**	***F***	***p***	**Partial η^2**
Channel Fz								
SO – σ CP Night (1 vs. 2)	68.80 (49.36), [60]	74.40 (53.08), [60]	3105.376	1	3105.375	3.784	.065	.147
Night X Age			2902.033	1	2902.033	3.537	.073	.138
Night X Log_AHI			11.685	1	11.685	0.014	.906	.001
Error (Night)			18052.784	22	820.581			
Channel Cz								
SO – σ CP Night (1 vs. 2)	18.40 (16.25), [20]	19.17 (15.01), [20] [a]	228.295	1	228.295	1.640	.214	.072
Night X Age			235.543	1	235.543	1.693	.207	.075
Night X Log_AHI			3.436	1	3.436	0.025	.877	.001
Error (Night)			2922.544	21	139.169			

Note. SO (0.5–1.25 Hz); σ, sigma, fixed bandwidth (9–13 Hz for Fz, 12–16 Hz for Cz). CP, absolute coupling phase distance from the SO up-state. *M*, Mean; *SD,* Standard Deviation; *Med,* Median. *F*-statistic, *p*-value, and Partial η^2 are for repeated-measures ANCOVA for CP with Night (1/baseline vs. 2/learning) as the repeated-measures factor. Age and apnea-hypopnea index (log-transformed; measured on Night 1) were included as covariates. Pearson's correlations revealed that values from the first to second overnight recording for each measure were more stable on Fz (r = 0.669, $p < .001$) relative to Cz (r = 0.427, p = .038). CP values on Cz were trimmed for extreme outliers: [a], n = 24.

Table S6

Between-night comparison of SO-sigma CP on SO events joined with a spindle (SO(+)) or not joined by a detected spindle (SO(-)) from Fz and Cz. N = 25.

	Baseline CP (*M* (*SD*), [*Med*]	**Learning CP (*M* (*SD*), [*Med*]**	**Type III SS**	**df**	**Mean Square**	***F***	***p***	**Partial η^2**
			Channel Fz					
SO(+) – σ CP Night (1 vs. 2)	81.60 (45.06), [60]	85.60 (47.44), [80]	8.371	1	8.371	0.010	.920	.000
Night X Age			57.645	1	57.645	0.071	.792	.003
Night X Log_AHI			532.388	1	532.388	0.657	.426	.029
Error (Night)			17832.135	22	810.522			
SO(-) – σ CP Night (1 vs. 2)	65.60 (51.16), [60]	72.80 (51.16), [60]	2153.860	1	2153.860	2.491	.129	.102
Night X Age			1778.848	1	1778.848	2.057	.166	.086
Night X Log_AHI			244.832	1	244.832	0.283	.600	.013
Error (Night)			19022.945	22	864.679			
			Channel Cz					
SO(+) – σ CP Night (1 vs. 2)	17.50 (12.25) , [20] [a]	22.50 (18.00), [20] [a]	13.208	1	13.208	0.087	.771	.004
Night X Age			18.385	1	18.385	0.121	.732	.006
Night X Log_AHI			131.276	1	131.276	0.863	.364	.041
Error (Night)			3041.277	20	152.064			
SO(-) – σ CP Night (1 vs. 2)	20.00 (19.15), [20]	23.20 (17.96), [20]	124.541	1	124.541	0.846	.368	.037
Night X Age			109.586	1	109.586	0.745	.397	.033
Night X Log_AHI			108.812	1	108.812	0.740	.399	.033
Error (Night)			3236.766	22	147.126			

Note. SO (0.5–1.25 Hz); σ, sigma, fixed bandwidth (9–13 Hz for Fz, 12–16 Hz for Cz). CP, absolute coupling phase distance from the SO up-state. SO(+) – σ reflects SO events joined with a detected spindle; SO(-) – σ reflects SO events not joined with a detected spindle. *F*-statistic, *p*-value,

and Partial η^2 are for repeated-measures ANCOVA for MI with Night (1/baseline vs. 2/learning) as the repeated-measures factor. Age and apnea-hypopnea index (log-transformed; measured on Night 1) were included as covariates. Pearson's correlations revealed highly stable values from the first to second overnight recording for each measure on Fz (SO(+): $r = 0.643$, $p = .001$, SO(-): $r = 0.670$, $p < .001$), but more modest stability on Cz (SO(+): $r = 0.304$, $p = .159$, SO(-): $r = 0.581$, $p = .002$). CP values on Cz were trimmed for extreme outliers on either night: [a], $n = 23$.

Table S7

Hierarchical regression to predict word-pair Consolidation Score by SO-sigma rel_MI from all SO events, SO events joined with a spindle (SO(+)), and SO events joined by a detected spindle (SO(-)) from Fz and Cz. N = 25.

Band pair	Channel Fz						Channel Cz					
	***F* (df)**	***p***	**ΔR^2**	***B* (*SE*)**	***β***	***p*(β)**	***F* (df)**	***p***	**ΔR^2**	***B* (*SE*)**	***β***	***p*(β)**
All SO												
SO – σ rel_MI	2.407 (3,19)	.099	0.064	-4.650 (3.594)	-.269	.211 [b]	1.784 (3,21)	.181	0.029	-2.321 (2.665)	-.187	.394
SO(+) and SO(-) sub-groups												
SO(+) – σ rel_MI	1.595 (3,20)	.222	0.004	-0.842 (2.677)	-.065	.756 [a]	**5.570 (3,21)**	**.006**	**0.269**	**-6.022 (1.891)**	**-.559**	**.004**
SO(-) – σ rel_MI	1.941 (3,19)	.157	0.023	-2.413 (3.191)	-.159	.459 [b]	1.500 (3,21)	.244	0.002	-0.576 (2.446)	-.050	.816

Note. SO (0.5–1.25 Hz); σ, sigma, fixed bandwidth (9–13 Hz for Fz, 12–16 Hz for Cz). rel_MI, change in Modulation Index between nights. SO(+) – σ reflects SO events joined with a detected spindle; SO(-) – σ reflects SO events not joined with a detected spindle. *F*-statistic, *p*-value, ΔR^2, *B (SE), β,* and *p(β)* are from hierarchical regression models (Model 2) with the rel_MI value of interest as the independent variable predicting word-pair consolidation in Model 2. Age and apnea-hypopnea index (log-transformed; measured on Night 1) were entered in Model 1. *p*(β) is p-value associated with the standardized regression coefficient for the independent variable, controlling for other model predictors. Values in **bold** denote results that reached or surpassed Bonferroni-adjusted *p*-value (.013). *B*, unstandardized coefficient. *β*, standardized coefficient; MI, modulation index; ΔR^2, change in proportion of explained variance; SE, standard error; *p*-value is for individual regression coefficient, controlling for other model predictors. [a], $n = 24$, [b], $n = 23$; 0-2 participants removed as outliers prior to analysis with rel_MI on Fz.

Table S8

Hierarchical regression to predict word-pair Consolidation Score by SO-sigma change in absolute distance from SO up-state (rel_CP) from all SO events, SO events joined with a spindle (SO(+)), and SO events joined by a detected spindle (SO(-)) from Fz and Cz. N = 25.

Band pair	Channel Fz						Channel Cz					
	***F* (df)**	***p***	**ΔR^2**	***B* (*SE*)**	***β***	***p*(*β*)**	***F* (df)**	***p***	**ΔR^2**	***B* (*SE*)**	***β***	***p*(*β*)**
All SO												
SO – σ rel_CP	**5.792 (3, 21)**	**.005**	**0.278**	**-0.108 (0.033)**	**-.569**	**.004**	1.716 (3, 20)	.196	0.002	-0.017 (0.092)	-.042	.841 [a]
SO(+) and SO(-) sub-groups												
SO(+) – σ rel_CP	1.478 (3, 21)	.249	0.000	-0.001 (0.041)	-.005	.979	1.719 (3, 20)	.195	0.002	-0.019 (0.088)	-.045	.828 [a]
SO(-) – σ rel_CP	**4.985 (3, 21)**	**.009**	**0.242**	**-0.098 (0.033)**	**-.518**	**.008**	1.478 (3, 21)	.249	0.000	0.001 (0.096)	.002	.994

Note. SO (0.5–1.25 Hz); σ, sigma, fixed bandwidth (9–13 Hz for Fz, 12–16 Hz for Cz). rel_CP, change in absolute coupling phase distance from the SO up-state between nights. SO(+) – σ reflects SO events joined with a detected spindle; SO(-) – σ reflects SO events not joined with a detected spindle. *F*-statistic, *p*-value, ΔR^2, *B (SE), β,* and *p*(*β*) are from hierarchical regression models with the rel_CP value of interest as the independent variable predicting word-pair consolidation in Model 2. Age and apnea-hypopnea index (log-transformed; measured on Night 1) were entered in Model 1. *p*(*β*) is *p*-value associated with the standardized regression coefficient for the independent variable, controlling for other model predictors. Values in **bold** denote results that reached or surpassed Bonferroni-adjusted *p*-value (.013). *B*, unstandardized coefficient. *β*, standardized coefficient; ΔR^2, change in proportion of explained variance; SE, standard error. [a] *n* = 24, 1 participant removed as an outlier prior to analysis with rel_CP on Cz.

Table S9

Hierarchical regression to predict word-pair Consolidation Score by SO-sigma MI and CP interaction on the learning night, from Fz and Cz. N = 25.

	Channel Fz						Channel Cz					
Band pair	***F* (df)**	***p***	**ΔR^2**	***B* (*SE*)**	***β***	***p*(*β*)**	***F* (df)**	***p***	**ΔR^2**	***B* (*SE*)**	***β***	***p*(*β*)**
SO – σ (base)												
MI [a]	-		-	-0.833 (1.354)	-.109	.546	-		-	-1.586 (1.360)	-.243	.258
CP [a]	-		-	**-0.102 (0.031)**	**-.680**	**.004**	-		-	-0.013 (0.082)	-.054	.872
MI x CP	**4.399 (5, 19)**	**.008**	**0.362**	**-0.043 (0.019)**	**-.384**	**.033**	2.435 (5, 19)	.073	0.216	-0.056 (0.033)	-.564	.107
SO – σ												
MI (Lower) [b]	-		-	-0.834 (1.354)	-.109	.545	-		-	-	-	-
CP [a]	-		-	-0.057 (0.035)	-.381	.120	-		-	-	-	-
MI(Low) x CP	-		-	**-0.043 (0.019)**	**-.461**	**.033**	-		-	-	-	-
SO – σ												
MI (Higher) [c]	-		-	-0.834 (1.354)	-.109	.545	-		-	-	-	-
CP [a]	-		-	**-0.146 (0.039)**	**-.978**	**.001**	-		-	-	-	-
MI(High) x CP	-		-	**-0.043 (0.019)**	**-.512**	**.033**	-		-	-	-	-

Note. SO (0.5–1.25 Hz); σ, sigma (fixed at 9–13 Hz for Fz, and at 12–16 Hz for Cz). MI, Modulation Index; CP, absolute coupling phase distance from the SO up-state. *F*-statistic, *p*-value, ΔR^2, *B (SE), β,* and *p*(*β*) are from hierarchical regression models to predict word-pair consolidation (Model 2) with centered MI and CP values included alongside a product term reflecting their interaction. Age and apnea-hypopnea index (log-transformed; measured on Night 1) were entered in Model 1. *F*-statistic and ΔR^2 is presented only for the final model with interaction term. ΔR^2, change in proportion of explained variance; SE, standard error. *B*, unstandardized coefficient. *β*, standardized coefficient. *p*(*β*) is *p*-value associated with the standardized regression coefficient for the independent variable, controlling for other model predictors. Values in **bold** denote results that surpassed the conventional critical *p*-value (< .05). "(base)" refers to the baseline interaction model, containing two mean-centered

predictors and their product as an interaction term; models in the two subsequent rows present follow-up analyses to examine moderating effects of MI when a significant interaction was found in the base model (See Figure 4). Note that regression coefficients for the moderator variable (MI) remain unchanged across each interaction model, whereas the unstandardized and standardized coefficients for CP are recalculated for each model; only the standardized coefficient for the interaction term changes across models. [a], mean-centered main-effect predictor; [b], mean-centered moderator adjusted down by 1 SD-unit (i.e., lower MI); [c], main-centered moderator adjusted up by 1 SD-unit (i.e., higher MI).

Table S10

Hierarchical regression to predict word-pair Consolidation Score by SO-sigma MI from all SO events from Fz and Cz during a combined N2+N3 stage on each night examined separately. N = 25.

Band pair	Channel Fz						Channel Cz					
	***F* (df)**	***p***	**ΔR^2**	***B* (*SE*)**	**β**	**$p_{(\beta)}$**	***F* (df)**	***p***	**ΔR^2**	***B* (*SE*)**	**β**	**$p_{(\beta)}$**
Baseline Night												
SO – σ MI	3.018 (3, 21)	.053	0.127	2.426 (1.242)	.368	.064	1.572 (3, 21)	.226	0.009	0.778 (1.607)	.100	.633
Learning Night												
SO – σ MI	1.634 (3, 21)	.212	0.015	0.980 (1.573)	.128	.623	1.478 (3, 21)	.249	0.000	-0.031 (1.334)	-.005	.982

Note. SO (0.5–1.25 Hz); σ, sigma, fixed bandwidth (9–13 Hz for Fz, 12–16 Hz for Cz). MI, Modulation Index. *F*-statistic, *p*-value, ΔR^2, *B (SE), β,* and *p*(*β*) are from hierarchical regression models with the MI value of interest (on each night separately) as the independent variable predicting word-pair consolidation in Model 2. Age and apnea-hypopnea index (log-transformed; measured on Night 1) were entered in Model 1. *p*(*β*) is *p*-value associated with the standardized regression coefficient for the independent variable, controlling for other model predictors. *B*, unstandardized coefficient. *β*, standardized coefficient; ΔR^2, change in proportion of explained variance; SE, standard error.

Table S11

Hierarchical regression to predict word-pair Consolidation Score by SO-sigma CP from all SO events from Fz and Cz during a combined N2+N3 stage on each night examined separately. N = 25.

Band pair	Channel Fz						Channel Cz					
	***F* (df)**	***p***	**ΔR^2**	***B* (*SE*)**	***β***	***p*(*β*)**	***F* (df)**	***p***	**ΔR^2**	***B* (*SE*)**	***β***	***p*(*β*)**
Baseline Night												
SO – σ CP	1.481 (3, 21)	.248	0.000	0.003 (0.034)	.020	.925	1.482 (3, 21)	.248	0.000	0.010 (0.098)	.021	.919
Learning Night												
SO – σ CP	**4.809 (3, 21)**	**.011**	**0.233**	**-0.094 (0.033)**	**-.631**	**.009**	1.849 (3, 20)	.171	0.014	0.059 (0.099)	.120	.557 [a]

Note. SO (0.5–1.25 Hz); σ, sigma, fixed bandwidth (9–13 Hz for Fz, 12–16 Hz for Cz). CP, absolute coupling phase distance from the SO up-state. *F*-statistic, *p*-value, ΔR^2, *B (SE), β,* and *p*(*β*) are from hierarchical regression models with the CP value of interest (on each night separately) as the independent variable predicting word-pair recall performance. Age and apnea-hypopnea index (log-transformed; measured on Night 1) were entered in Model 1. Values in **bold** denote results that reached or surpassed Bonferroni-adjusted *p*-value (.013). *p*(*β*) is *p*-value associated with the standardized regression coefficient for the independent variable, controlling for other model predictors. *B*, unstandardized coefficient. *β*, standardized coefficient; ΔR^2, change in proportion of explained variance; SE, standard error. [a], *n* = 24; 1 participant removed as an outlier prior to analysis with CP on Cz.

Table S12

Between-night comparison of SO-sigma MI from all SO events from Fz and Cz during stage N2 and N3 considered separately. N = 25.

	Baseline MI (*M* (*SD*), [*Med*])	Learning MI (*M* (*SD*), [*Med*])	Type III SS	df	Mean Square	*F*	*p*	Partial η^2
Stage N2								
Channel Fz								
SO – σ MI, Night (1 vs. 2)	-8.79 (1.15), [-8.89]	-8.95 (0.97), [-9.26]	1.090	1	1.090	3.650	.069	.142
Night X Age			0.643	1	0.643	2.153	.156	.089
Night X Log_AHI			1.695	1	1.695	5.675	.026	.205
Error (Night)			6.571	22	0.299			
Channel Cz								
SO – σ MI, Night (1 vs. 2)	-7.32 (0.99), [-7.20]	-7.60 (1.25), [-7.41]	0.559	1	0.559	3.002	.097	.120
Night X Age			0.282	1	0.282	1.513	.232	.064
Night X Log_AHI			0.821	1	0.821	4.406	.048	.167
Error (Night)			4.098	22	0.186			
Stage N3								
Channel Fz								
SO – σ MI, Night (1 vs. 2)	-7.95 (0.94), [-7.81]	-8.17 (1.15), [-8.38]	0.447	1	0.447	1.868	.186	.078
Night X Age			0.217	1	0.217	0.909	.351	.040
Night X Log_AHI			0.849	1	0.849	3.551	.073	.139
Error (Night)			5.262	22	0.239			
Channel Cz								
SO – σ MI, Night (1 vs. 2)	-6.41 (0.87), [-6.32]	-6.60 (0.94), [-6.42]	0.076	1	0.076	0.335	.569	.015
Night X Age			0.024	1	0.024	0.106	.748	.005
Night X Log_AHI			0.196	1	0.196	0.864	.363	.038
Error (Night)			4.986	22	0.227			

Note. SO, slow oscillation (0.5–1.25 Hz); σ, sigma, fixed bandwidth (9–13 Hz for Fz, 12–16 Hz for Cz). MI, Modulation Index. *M*, Mean; *SD,* Standard Deviation; *Med,* Median. *F*-statistic, *p*-value, and Partial η^2 are for repeated-measures ANCOVA with Night (1/baseline vs. 2/learning) as the repeated-measures factor. Age and apnea-hypopnea index (log-transformed; measured on Night 1) were included as covariates. Pearson's correlations revealed highly stable values from the first to second overnight recording for each measure on Fz (N2: $r = 0.676$, $p < .001$; N3: $r = 0.774$, $p < .001$) and on Cz (N2: $r = 0.851$, $p < .001$; N3: $r = 0.738$, $p < .001$).

Table S13

Between-night comparison of SO-sigma CP from all SO events from Fz and Cz during stage N2 and N3 considered separately. N = 25.

	Baseline MI (*M* (*SD*), [*Med*])	Learning MI (*M* (*SD*), [*Med*])	Type III SS	df	Mean Square	*F*	*p*	Partial η^2
Stage N2								
Channel Fz								
SO – σ CP, Night (1 vs. 2)	81.60 (48.28), [80]	91.20 (53.88), [80]	2424.484	1	2424.484	2.798	.109	.113
Night X Age			2158.789	1	2158.789	2.492	.129	.102
Night X Log_AHI			4.275	1	4.275	0.005	.945	.000
Error (Night)			19059.975	22	866.362			
Channel Cz								
SO – σ CP, Night (1 vs. 2)	20.00 (18.65), [20]	22.50 (18.00), [20][a]	61.697	1	61.697	0.556	.464	.026
Night X Age			45.520	1	45.520	0.410	.529	.019
Night X Log_AHI			137.927	1	137.927	1.243	.277	.056
Error (Night)			2329.575	21	110.932			
Stage N3								
Channel Fz								
SO – σ CP, Night (1 vs. 2)	56.80 (44.23), [60]	53.60 (45.72), [40]	2409.437	1	2409.437	4.232	.052	.161
Night X Age			2541.758	1	2541.758	4.464	.046	.169
Night X Log_AHI			2.600	1	2.600	.005	.947	.000
Error (Night)			12526.238	22	569.374			
Channel Cz								
SO – σ CP, Night (1 vs. 2)	20.83 (18.16), [20]	28.33 (21.20), [20][a]	14.773	1	14.773	0.037	.849	.002
Night X Age			2.193	1	2.193	0.006	.941	.000
Night X Log_AHI			3.826	1	3.826	0.010	.923	.000
Error (Night)			8318.509	21	396.119			

Note. SO (0.5–1.25 Hz); σ, sigma, fixed bandwidth (9–13 Hz for Fz, 12–16 Hz for Cz). CP, absolute coupling phase distance from the SO up-state. *M*, Mean; *SD,* Standard Deviation; *Med,* Median. *F*-statistic, *p*-value, and Partial η^2 are for repeated-measures ANCOVA for CP with Night (1/baseline vs. 2/learning) as the repeated-measures factor. Age and apnea-hypopnea index (log-transformed; measured on Night 1) were included as covariates. Pearson's correlations revealed that values from the first to second overnight recording for each measure were more stable on Fz (N2: $r = 0.666$, $p < .001$; N3: $r = 0.690$, $p < .001$) relative to Cz (N2: $r = 0.674$, $p < .001$; N3: $r = 0.072$, $p = .740$). [a], $n = 24$, 1 participant removed as an outlier prior to analysis with CP on Cz.

Table S14

Hierarchical regression to predict word-pair Consolidation Score by SO-sigma rel_MI from all SO events from Fz and Cz during stages N2 and N3 examined separately. N = 25.

Band pair	Channel Fz						Channel Cz					
	***F* (df)**	***p***	**ΔR^2**	***B* (*SE*)**	***β***	***p*(*β*)**	***F* (df)**	***p***	**ΔR^2**	***B* (*SE*)**	***β***	***p*(*β*)**
Stage N2												
SO – σ rel_MI	3.663 (3, 20)	.030	0.166	-5.987 (2.643)	-.414	.035[a]	1.683 (3, 21)	.201	0.020	-1.896 (2.660)	-.158	.484
Stage N3												
SO – σ rel_MI	2.300 (3, 21)	.107	0.073	-3.237 (2.268)	-.298	.168	2.224 (3, 21)	.115	0.067	-3.181 (2.340)	-.264	.188

Note. SO (0.5–1.25 Hz); σ, sigma, fixed bandwidth (9–13 Hz for Fz, 12–16 Hz for Cz). rel_MI, change in Modulation Index between nights. *F*-statistic, *p*-value, ΔR^2, *B (SE), β,* and *p*(*β*) are from hierarchical regression models with the rel_MI value of interest as the independent variable predicting word-pair consolidation in Model 2. Age and apnea-hypopnea index (log-transformed; measured on Night 1) were entered in Model 1. *p*(*β*) is *p*-value associated with the standardized regression coefficient for the independent variable, controlling for other model predictors. *B*, unstandardized coefficient. *β*, standardized coefficient; ΔR^2, change in proportion of explained variance; SE, standard error. [a], *n* = 24; 1 participant removed as an outlier prior to analysis with rel_MI on Fz.

Table S15

Hierarchical regression to predict word-pair Consolidation Score by SO-sigma change in absolute distance from SO up-state (rel_CP) from all SO events from Fz and Cz during stages N2 and N3 examined separately. N = 25.

Band pair	Channel Fz						Channel Cz					
	***F* (df)**	***p***	**ΔR^2**	***B* (*SE*)**	***β***	***p*(*β*)**	***F* (df)**	***p***	**ΔR^2**	***B* (*SE*)**	***β***	***p*(*β*)**
Stage N2												
SO – σ rel_CP	1.858 (3, 21)	.168	0.035	-0.037 (0.039)	-.199	.343	1.700 (3, 20)	.199	0.000	-0.005 (0.103)	-.010	.961 [a]
Stage N3												
SO – σ rel_CP	1.552 (3, 21)	.231	0.007	-0.021 (0.048)	-.093	.672	1.497 (3, 21)	.244	0.002	-0.012 (0.054)	-.043	.830

Note. SO (0.5–1.25 Hz); σ, sigma, fixed bandwidth (9–13 Hz for Fz, 12–16 Hz for Cz). rel_CP, change in absolute coupling phase distance from the SO up-state between nights. *F*-statistic, *p*-value, ΔR^2, *B (SE), β,* and *p*(*β*) are from hierarchical regression models with the rel_CP value of interest as the independent variable predicting word-pair consolidation in Model 2. Age and apnea-hypopnea index (log-transformed; measured on Night 1) were entered in Model 1. *P*(*β*) is *p*-value associated with the standardized regression coefficient for the independent variable, controlling for other model predictors. *B*, unstandardized coefficient. *β*, standardized coefficient; ΔR^2, change in proportion of explained variance; SE, standard error. [a] *n* = 24, 1 participant removed as an outlier prior to analysis with rel_CP on Cz.

Table S16

Circular statistics of SO-sigma raw coupling phase between experimental nights on Fz and Cz, from all SO events during stages N2 and N3 examined separately. N = 25.

	Baseline				Learning				Between Nights		Circular-Linear Correlation with Memory Consolidation	
	Angle	**R**	**Z**	$p_{(Z)}$	**Angle**	**R**	**Z**	$p_{(Z)}$	$F_{(W\text{-}W)}$	$p_{(W\text{-}W)}$	***r***	***p***
Channel Fz												
SO – σ, Stage N2	3.79	0.02	37.62	.023	4.07	0.02	33.25	.032	1.051	.020	0.16	.724
SO – σ, Stage N3	4.64	0.03	18.83	.132	4.89	0.03	19.43	.031	-	-	0.20	.611
Channel Cz												
SO – σ, Stage N2	4.41	0.05	94.77	.012	4.25	0.05	82.63	.011	0.093	.396	0.42	.114
SO – σ, Stage N3	4.35	0.07	57.13	.016	4.32	0.07	56.20	.024	0.149	.537	0.51	.039

Note. SO, slow oscillation (0.5–1.25 Hz); σ, sigma, fixed bandwidth (9–13 Hz for Fz, 12–16 Hz for Cz). *Angle* and *R* are the group average direction and length of the resultant vector of the coupling phase distribution, respectively. *Z*-statistic and associated *p*-value are the group average for the Rayleigh test for non-uniformity of a circular distribution. Between-night differences in raw coupling phase was examined using a Watson-Williams test for unequal means in circular distributions, with associated *F*-statistic and *p*-value. Watson-Williams test was only performed when the Rayleigh test showed significant coupling on both nights at $p < .05$. There was one trend-level difference in raw SO – σ coupling phase between nights for measures from channel Fz during stage N2. Circular-linear correlations between raw coupling phase and memory consolidation is specific to coupling phase from the learning-task night only. There was one trend-level correlation with memory for raw SO – σ coupling phase from channel Cz during stage N3.

Table S17

Between-night comparison of NREM SO and sigma power spectral density (PSD) from Fz and Cz. N = 25.

	Baseline *M* (*SD*)	Learning *M* (*SD*)	Type III SS	df	Mean Square	*F*	*p*	Partial η^2
Channel Fz								
SO (n.u.) Night (1 vs. 2)	-0.0028 (0.0004)	-0.0028 (0.0005)	< 0.001	1	< 0.001	0.042	.839	.002
Night X Age			< 0.001	1	< 0.001	0.064	.803	.003
Night X Log_AHI			< 0.001	1	< 0.001	6.569	.018	.230
Error (Night)			< 0.001	22	< 0.001			
σ (n.u.) Night (1 vs. 2)	-0.0004 (0.0019)	-0.0002 (0.0017)	< 0.001	1	< 0.001	0.625	.438	.028
Night X Age			< 0.001	1	< 0.001	0.122	.730	.006
Night X Log_AHI			< 0.001	1	< 0.001	4.461	.046	.169
Error (Night)			< 0.001	22	< 0.001			
Channel Cz								
SO (n.u.) Night (1 vs. 2)	-0.0028 (0.0004)	-0.0027 (0.0005)	< 0.001	1	< 0.001	0.657	.426	.029
Night X Age			< 0.001	1	< 0.001	0.334	.569	.015
Night X Log_AHI			< 0.001	1	< 0.001	1.696	.206	.072
Error (Night)			< 0.001	22	< 0.001			
σ (n.u.) Night (1 vs. 2)	0.0015 (0.0015)	0.0017 (0.0014)	< 0.001	1	< 0.001	0.889	.356	.039
Night X Age			< 0.001	1	< 0.001	0.221	.643	.010
Night X Log_AHI			< 0.001	1	< 0.001	2.937	.101	.118
Error (Night)			< 0.001	22	< 0.001			

Note. SO, Slow Oscillation power (0.5–1.25 Hz); σ, sigma, fixed bandwidth (9–13 Hz for Fz, 12–16 Hz for Cz); n.u.; normalized units; *F*-statistic, *p*-value, and Partial η^2 are for repeated-measures ANCOVA with Night (baseline vs. learning) as the repeated-measures factor. Age and apnea-hypopnea index (log-transformed) were included as covariates.

Table S18

Hierarchical regression to predict word-pair Consolidation Score by SO-sigma change in PSD between nights from Fz and Cz. N = 25.

PSD	Channel Fz						Channel Cz					
	***F* (df)**	***p***	**ΔR^2**	***B* (*SE*)**	***β***	***p*(*β*)**	***F* (df)**	***p***	**ΔR^2**	***B* (*SE*)**	***β***	***p*(*β*)**
SO (n.u.)	1.622 (3, 21)	.214	0.072	3345.81 (5602.445)	.134	.557	1.549 (3, 21)	.231	0.007	-1935.29 (4604.287)	-.087	.679
σ (n.u.)	1.988 (3, 21)	.147	0.047	2768.83 (2462.509)	.239	.274	1.723 (3, 21)	.193	0.023	3279.22 (4210.613)	.163	.445

Note. SO, Slow Oscillation power (0.5–1.25 Hz); σ, sigma, fixed bandwidth (9–13 Hz for Fz, 12–16 Hz for Cz); n.u.; normalized units. *F*-statistic, *p*-value, ΔR^2, *B (SE), β,* and *p(β*) are from hierarchical regression models with the PSD measure of interest as the independent variable predicting word-pair consolidation in Model 2. Age and apnea-hypopnea index (log-transformed, measured on Night 1) were entered in Model 1. *p*(*β*) is *p*-value associated with the standardized regression coefficient for the independent variable, controlling for other model predictors. *B*, unstandardized coefficient. *β*, standardized coefficient; ΔR^2, change in proportion of explained variance; SE, standard error.

Transition from Study 1 to Study 2

Multiple recent studies have demonstrated, using a variety of methods, a typical pattern of coupling between spindle activity (σ) and the slow oscillation (SO) phase, and associations between SO – σ CFC and memory consolidation. There is a growing theory that reduced or impaired SO – σ coupling with greater age is a neural mechanism of ageing-related cognitive impairments; however, this hypothesis is still generating support, as there is only a handful of studies available do examine SO – σ CFC in middle-aged (Bartsch et al., 2019; Demanuele et al., 2017; Mylonas et al., 2020) and older adults (Djonlagic et al., 2021; Ladenbauer et al., 2017; See also Sattari et al., 2019; Sunwoo et al., 2021; and Winer et al. 2019), and only 4 studies appear available to directly compare SO – σ CFC between younger and older adults in the context of memory (Helfrich et al., 2018; Ladenbauer et al., 2021; Muehlroth et al., 2019; Schneider et al., 2021). In turn, my Study 1 added to the current literature base by providing a thorough examination of SO – σ CFC during non-rapid-eye-movement (NREM) sleep in healthy older adults, and relations between coupling with learning and declarative (word-pair) memory performance.

We gleaned several conceptual and methodological insights from Study 1. First, it is possible that SO – σ CFC reflects a trait-like, individual-difference in neural activity. Second, SO-slow-spindle CFC may continue to support overnight memory consolidation in older age, which is a novel finding given that most current discussions of SO – σ CFC emphasize the memory-associated benefits of fast spindle coupling. Third, results of an exploratory interaction model supported a perspective that coupling strength and coupling phase may both make their own contributions to the memory consolidation process, at least in older adults. Fourth, relations between CFC and memory may be clarified by examining coupling among co-occurring SO-spindle complexes versus isolated SO events.

The findings in Study 1 provide a detailed snapshot of coupled brain activity in healthy older adults during NREM sleep. However, while this study helps to fill a noteworthy gap in the extant CFC literature, it was not without its limitations; namely, the lack of a young adult control group, using an initial screening night as a non-learning baseline, and lacking a cognitive control task. In reflecting on the process and outcome of Study 1, my second study was designed with the intention of expanding and

replicating my initial analyses in a 3-night protocol using a new sample of older adults, and making direct comparisons with a young adult group and with a cognitive control task to match our word-pair task.

Study 1 also provided a brief review of the current state of this research field, with a specific focus on the disparate methods used across studies to measure and analyze coupling metrics. A particular point was raised about spindle frequency bands selected for analysis, where I highlighted that more recent studies are gravitating away from the use of a fixed sigma power bandwidth applied to all subjects, and instead towards the use of individually adapted bands. The use of adapted bands follows from previous observations of spindles evidencing strong intra-individual, but not inter-individual, night-to-night consistency (e.g., in frequency, density; Cox et al., 2017; Eggert et al., 2015; Ujma et al., 2015). Moreover, studying CFC with adapted bands accounts for individual differences in sleep oscillations related to unique brain-ageing trajectories, and conforms with recommendations to design "age-fair" protocols in studies with older populations (Muehlroth et al., 2020). Considering this, it would be reasonable to anticipate that measures of coupled brain activity, and their relations with memory, would be more accurately captured when metrics are derived while considering that not every brain functions the same, which may be especially pertinent in ageing research. In turn, my Study 2 also aimed to account for individual differences in oscillation activity, by comparing results between CFC measures derived in a fixed-band condition (as in Study 1) and measures derived using individually adapted frequency bands based on spindle power peaks.

The Impact of Ageing on Slow Oscillation-Spindle Cross-Frequency Coupling during Non-Rapid-Eye-Movement Sleep

Oren M. Weiner[1,2] and Thien Thanh Dang-Vu[1,2,3]

[1]PERFORM Center and Center for Studies in Behavioural Neurobiology, Department of Psychology and Department of Health, Kinesiology, and Applied Physiology, Concordia University

[2]Centre de Recherche de l'Institut Universitaire de Gériatrie de Montréal, CIUSSS Centre-Sud-de-l'île-de-Montréal

[3]Department of Neurosciences, Université de Montréal

Abstract

Ageing coincides with multiple changes in brain activity and behaviour, such as weaker or aberrant neural oscillations, changes in sleep quality and quantity, and cognitive impairment. Cross-frequency coupling (CFC) of slow oscillations (SO) and spindles during non-rapid-eye-movement (NREM) sleep may facilitate overnight memory consolidation, however it remains unclear how this association is impacted by ageing. This study used a 3-night protocol that included both a sleep-dependent word-pair memory task and a non-learning control task. Sixteen healthy young adults (*M* (SD) age = 24.50 (3.31) years; 56.3% female) and 16 healthy older adults (*M* (SD) age = 67.44 (6.81) years; 68.8% female) completed the study. Measures of SO-slow-spindle coupling strength and coupling phase distance from the SO up-state were examined from Fz for between-group and across-night differences and tested for associations with memory. Analyses were conducted with coupling measures derived using both a fixed frequency band and with individually adapted bands. Our main analyses show that coupling strength did not differ across groups or nights, and coupling phase distance was stable across nights. Coupling phase distance was significantly different between groups, with a peak in young adults positioned closer to the down-state and in older adults positioned closer to the up-state. CFC was not significantly associated with memory in our main analyses. This study adds supporting evidence for an ageing-related decline in precise SO-spindle coupling but was unable to demonstrate that coupling was associated with memory in either group. Results are discussed in reference to ageing effects on NREM CFC, and to the discrepant patterns of results across our different analytic approaches.

The Impact of Ageing on Slow Oscillation-Spindle Cross-Frequency Coupling during Non-Rapid-Eye-Movement Sleep

Phase-amplitude cross-frequency coupling (CFC) between cardinal non-rapid-eye-movement (NREM) sleep oscillations has amassed interest as a potential mechanism of overnight memory consolidation. Accumulating evidence, mostly from studies with young adults, suggests that faster centro-parietal spindles (12–16 Hz) are maximal during or surrounding the slow oscillation (SO; < 1 Hz) depolarizing up-state peak, while slower frontal spindles (9–13 Hz) peak more during the up-to-down-state transition phase; this coordinated timing, particularly with fast spindle power, is thought to facilitate overnight memory consolidation (Bartsch et al., 2019; Dehnavi et al., 2021; Hahn et al., 2020 and 2022; Helfrich et al., 2018; Ladenbauer et al., 2017; Mikutta et al., 2019; Muehlroth et al., 2019; Niknazar et al., 2015; Zhang et al., 2020). More recent studies have also demonstrated that SO and spindle oscillations are themselves coupled with hippocampal (HC) ripple activity (e.g., 80–90 Hz; Dickey et al., 2021). Ripples are prominent during slow-wave-sleep (Eschenko et al., 2008; Jiang et al., 2019a) and thought to reflect "offline" neural traces of wakeful experiences (Cross et al., 2018; Le Van Quyen et al., 2010; Piantoni et al., 2013; Valderrama et al., 2012). A triple-phase-locking of cortical SOs, thalamo-cortical (TC) spindles, and HC sharp-wave ripples is proposed as a mechanism for an "active systems" model of memory consolidation during sleep; this model posits that repeated co-reactivations of memory representations (or "engrams") in the neocortex and HC during sleep facilitate the transfer of memories from temporary HC stores to more permanent and HC-independent cortical networks (e.g., Geva-Sagiv & Nir, 2019; Helfrich et al., 2019; Klinzing et al., 2019; Rasch & Born, 2013).

Electroencephalogram (EEG) studies of NREM CFC have largely focused on coupling between the phase of cortical SOs and amplitude of TC spindle activity. Studies demonstrate that spindle activity locked with the SO up-state is associated with better memory in young adults (Mikutta et al., 2019; Mölle et al., 2009; Ruch et al., 2012). A handful of studies also demonstrate that specific interventions during sleep can optimize this SO-spindle timing and improve memory (e.g., auditory stimulation (Krugliakova et al., 2020); targeted memory reactivation with olfactory (Bar et al., 2020) or auditory cueing (Schreiner

et al., 2018); drug vs. placebo (Niknazar et al., 2015; Zhang et al., 2020). Most of these intervention studies were with young adults, however one study in older adults (Ladenbauer et al., 2017) demonstrated that transcranial direct current stimulation (tDCS) optimized SO – (fast) σ timing and improved visual recognition memory in seniors with mild cognitive impairment (MCI). As well, Dehnavi et al. (2021) reported that their measure of SO-slow spindle coupling strength (with the SO trough) at a baseline was correlated with improved word-pair overnight retention following electrical stimulation during N3. Together, these results provide an interesting foundation for developing non-invasive or pharmacological interventions that capitalize on brain oscillations and their coupling during sleep to promote cognition.

Ageing coincides with neuroanatomical, neurophysiological, and behavioural changes associated with sleep (Buysee et al., 2005; Steiger, 2007). Older adults spend more time in N1 sleep, less time in N3 and REM sleep, and have more arousals across sleep stages versus teenage or middle-aged participants (Boselli et al., 1998; Munch et al., 2004; see also Ohavon et al., 2004). Unsurprisingly, older adults experience more difficulty with their sleep and have more sleep-related complaints than young adults, and there is a higher incidence of sleep disorders in the elderly, including more insomnia symptoms, sleep apnea, and restless legs syndrome (Morrell et al., 2012; Stanley, 2005). Sleep disturbances are also commonly seen among older adults with cognitive decline and neurodegeneration (Mayer et al., 2011; Shub et al., 2009), and may be a risk factor for developing dementia symptoms (Benedict et al., 2015; Lim et al., 2013). A growing hypothesis of how poor sleep could promote dementia involves disruptions to the brain's glymphatic system, which normally acts during (slow-wave) sleep to clear excess proteins and metabolic wastes that accumulate during wakefulness (e.g., β-amyloid levels associated with Alzheimer's pathology; Hauglund et al., 2020; Nedergaard & Goldman, 2020; Ooms et al., 2014).

Chronic difficulties with sleep onset and/or sleep maintenance are associated with deficits in episodic memory, problem solving, and/or working memory (see Fortier-Brochu et al., 2011 for a meta-analysis). As well, longitudinal studies demonstrate that worsening self-reported insomnia symptoms across several years (e.g., difficulties falling asleep, early waking, short sleep duration) independently predicts cognitive decline in older adults (Cricco et al., 2001; Keage et al., 2012), and perhaps specifically

related to subjective memory declines (Zhao et al., 2022). Ageing also coincides with changes in sleep micro-architecture, such as decreased slow wave activity (SWA) and sigma power, and decreased density and amplitude of SOs and sleep spindles (Crowley et al., 2002; Gaudreau et al., 2001; see also Edwards et al., 2010 and Fogel et al., 2012 for reviews), which may contribute more directly to memory impairments and AD symptomology (Mander et al., 2013, 2014, and 2015). Together, results suggest that age-related declines in sleep and sleep oscillations at least partially explain memory impairments seen with normal ageing. It is hypothesized that ageing-related declines in SO – σ CFC are a more specific mechanism of this association (Helfrich et al., 2018; Muehlroth et al., 2019), and that measures of CFC could act as potential biomarkers of cognitive decline in MCI or Alzheimer's disease (AD; Weng et al., 2020).

Studies of NREM coupling and memory have increased in popularity across the last two decades, although examinations of age-group differences in coupling dynamics and relations with memory are more recent. To our knowledge there are only a small handful of studies available that directly compare SO – σ CFC between younger and older adult samples (Helfrich et al., 2018; Ladenbauer et al., 2021; Muehlroth et al., 2019; Schneider et al., 2020). Evidence from these studies suggest that fast spindle activity peaks earlier in the SO rising phase in older versus younger adults, and that this mistiming in aged samples is associated with worse memory. Further evidence for an ageing effect on CFC (i.e., earlier coupling with greater age) comes from a recent epidemiological study with two large cohorts of older adults (Djonlagic et al., 2021), and from a study by Sunwoo and colleagues (2021) between older adults with and without idiopathic REM-sleep behaviour disorder. Of note, many studies of SO – σ and memory, including in the context of ageing (e.g., Helfrich et al., 2018; Muehlroth et al., 2019), often rely on or showcase only one sleep recording visit for analysis. This kind of study design precludes examination of if the observed coupling reflects an increase, decrease, or null change from a baseline or control condition, and limits interpretations about CFC as a constant/stable trait versus a reflection of brain activity that is responsive to pre-sleep experience. Many studies also often use a fixed spindle frequency range for CFC analysis, which assumes that all participants' brain activity is the same; by contrast, adapting spindle frequency bands allows one to account for subtle individual differences. Lastly,

studies differ in the memory tests that are used, such as in the type of memory examined (e.g., declarative vs. procedural), type of testing (e.g., recognition vs. recall), and learning load of the test (e.g., 40 vs. 120 word-pairs). Thus, it remains unclear if similar relations with memory across younger and older groups exist when SO – σ CFC is examined in the context of a learning versus control task paradigm, when measured using adapted frequency bands, and in the context of recall memory (vs. recognition).

Given the general paucity of studies directly examining SO – σ CFC and memory in ageing, this study compared SO – σ coupling strength and coupling phase between healthy young and older adults, and between two experimental nights of sleep (learning vs. control) that followed an initial baseline screening. This 3-night study design allows for examining both within- and between-subject effects regarding CFC and memory in ageing, while also accounting for potential first-night effects. This study had three specific aims: First, we examined age-group (younger vs. older) and across-night (learning vs. control) differences in SO – σ CFC. For this we hypothesized that older adults would evidence less coupling strength and a mis-timed (i.e., earlier) preferred coupling phase profile compared to younger adults, and that there would be learning-induced modulations in coupling that are more evident in the younger sample. Second, we examined if a measure of change in SO – σ CFC between experimental nights can predict memory consolidation scores on our word-pair associates task. For this, and building on Study 1, we hypothesized that relations between CFC and declarative memory would be stronger for our measure of coupling phase distance from the up-state than for measures of coupling strength. More specifically, we hypothesized that a SO-slow-spindle coupling phase closer to the up-state would predict better memory consolidation in the OA group, given the findings of Study 1, and previous observations of slow spindle power coupling earlier in the SO up-to-down-state phase compared to young adults (e.g., Ladenbauer et al., 2021; Muehlroth et al., 2019). Finally, this study replicated the exploratory interaction analysis from Study 1 by repeating the same model using an independent sample of older adults and comparing this with results from the young adult group; we hypothesized the same moderating effect of coupling strength on the relation between CP and memory consolidation, but with no *a priori* hypothesis made about differences in the association or effect sizes between age-groups.

Throughout the analyses described above, an additional comparison was drawn between measures that were derived considering fixed versus individually adapted spindle frequency bands. Complementary measures of CFC were derived using two approaches: (1) a fixed-frequency applied for all participants, and (2) an individualized adapted-frequency band (based on sigma spectral peaks). An overarching hypothesis was that adapted-band measures would show more varied coupling phase patterns across participants and stronger associations with memory, given that these measures would better capture the individual differences in brain activity and coupling dynamics across subjects.

Following these primary study aims, supplemental analyses further expanded our examination by considering similar analyses for data measured from the cortical vertex (Cz) and from overlapping SO-spindle complexes, as well as circular data from the measures of raw coupling phase, and measures of power spectral density in component frequency bands.

Materials and Methods

The recruitment and screening, overnight sleep recording, cognitive testing, and EEG pre-processing and analysis procedures in this study are largely overlapping with those described in Study 1. Reported below are pertinent procedural details of this study. Methodological differences in the protocol relate to the inclusion of 1) healthy older adults and healthy young adults, 2) an additional (3rd) recording night with a cognitive control task, and 3) Developments made to specific aspects of our EEG analysis pipeline. The reader is referred to Study 1 for more complete details of the remaining study methods.

Recruitment and Screening Procedure

Young and older adults who identified as healthy and good sleepers were recruited for this study from the general Montreal community. Interested volunteers were evaluated in a two-stage process, involving (1) a brief, telephone-based screening interview, and (2) an in-person assessment of sleep and general health, and to screen cognitive functioning.

Young adults (18–30 years-old) and older adults (55–85 years-old) were screened based on the same criteria used in Study 1, with some specific modifications (described below). During the in-person interview, volunteers were similarly evaluated for eligibility based on the Mini Mental State Exam

(MMSE; Crum et al., 1993; Magni et al., 1996; Tombaugh & McIntyre, 1992) and Montreal Cognitive Assessment (MoCA; Nasreddine et al., 2005; Rossetti et al., 2011), and a battery of self-report questionnaires. Volunteers were excluded after the interview if they scored < 26 on the MMSE and < 24 on the MoCA. Volunteers were also evaluated using the same self-report questionnaires as in Study 1, with the following exceptions. First, for the Morningness-Eveningness Questionnaire (MEQ; Horne & Östberg, 1976; Taillard et al., 2004), an exclusionary cut-off for young adults was obtaining a score of ≤ 30, "Very Morning" and ≥ 70, "Very Evening"; for older adults, only "Very Evening" types were excluded, as we anticipated older adults to keep a generally earlier sleep/wake schedule. Second, while older adults were evaluated based on pre-defined cut-scores on the Geriatric Depression Scale (≥ 15; Yesavage et al., 1982) and Geriatric Anxiety Inventory (≥ 10; Pachana et al., 2007), young adults were evaluated using the Beck Depression Inventory (≥ 15; Beck et al., 1996) and Beck Anxiety Inventory (≥ 10; Beck et al., 1993). If eligible following the interview, participants were scheduled for an overnight PSG recording, used to rule out underlying sleep disorders.

Twenty-seven young adults and 30 older adults were eligible following the in-person screening and scheduled for a PSG recording. Importantly, older adults were excluded after their PSG night if they evidenced any more than mild sleep apnea, defined as an apnea-hypopnea index (AHI) > 15/hr. All young adults had an AHI < 5/hr except for one participant with an AHI of ~7/hr. Individuals deemed fully eligible after their PSG visit were then scheduled to return at least 7 days later to complete the second (electroencephalogram, EEG) recording visit (EEG1), and at least 7 days after that for their third and final visit (EEG2). A total of 25 young adults and 18 older adults were deemed eligible and scheduled to complete the remaining 2 recording visits and cognitive tasks. Three otherwise eligible young adults were excluded after their first PSG night for evidencing atypical or otherwise poor sleep during intervening weeks, and three young adults withdrew before completing the study. Two young adults were excluded following their first recording, one for having revealed cannabis use, and another after a review of their initial sleep recording indicated mild sleep apnea. Two older adults were excluded after their PSG night because of a change in eligibility due to medication or due to especially poor performance on the word-

pair task (i.e., pre-sleep test score of ≤ 5 points). To maintain a balanced sample between the two groups, a total of 16 young adults and 16 older adults were included in the final analyses.

Study Protocol

The study protocol is displayed in Figure 1. Participants were scheduled to arrive at the sleep lab for each recording visit between 7pm and 9pm. The procedures of the first (baseline/PSG) night are otherwise identical to Study 1. As in Study 1, participants completed sleep diaries and were monitored by wrist actigraphy between each study visit. The second and third overnight visits each included EEG sleep recordings but with less equipment compared to the PSG night (see below). These subsequent visits both included pre- and post-sleep cognitive testing like in Study 1, with exception here that one of these testing nights included a memory test and the other night included a non-learning control task. Task order was randomized/counterbalanced between nights across participants; this allowed participants to serve as their own control in examining relations of coupling with learning and memory. Before starting either task, participants viewed a 5–10-minute resting baseline video (nature movie). Each task included an instruction period, learning or practice phase, and both a pre-sleep and post-sleep testing period. Participants also completed an N-back and a Go/no-go task at the end of each post-sleep/AM testing interval (data not reported). After finishing all three morning tasks on the final study visit, participants were disconnected from equipment and offered monetary compensation.

Participants were instructed to abstain from drinking alcohol or excessive caffeine intake within the 24-hours before each study visit. Sleep diary entries were reviewed with participants on both the 2nd and 3rd recording visit to ensure a stable and "normal/typical" sleep/wake pattern across the previous week. As well, young adults who were current students were scheduled accordingly to minimize any overlap with exams or other major assignments. All sleep studies took place in a private research bedroom in our sleep laboratory. All study procedures and documents were approved by ethics committees at both Concordia University and CRIUGM, and all participants signed an informed consent form prior to starting the study.

Cognitive Testing

Word-Pair Associates

The primary task used in this study is a variant of the word-pair associates task (Backhaus et al., 2007; Plihal & Born, 1997). The task was otherwise identical to that used in Study 1, with the exception being that a new list of 40 pairs was generated (using similar criteria for word length, frequency, and emotionality). Equivalent lists were developed in both English and French. Participants were tested in either French or English, depending on which language they learned first and were more comfortable with using in daily life. After all word-pairs were presented twice, participants underwent a short-delay cued-recall trial, where they were shown the first word in a pair on the screen and asked to recall the second word verbally. A research assistant was present to score verbal responses. Participants were given unlimited time to provide an answer. No feedback was given to participants after responding. The post-sleep (AM recall) test began an average of 37.06 minutes after Lights On (range = 12-87 minutes). The primary outcome variable was a measure of overnight memory consolidation, calculated as the number of correct word-pair responses involving the *same* word-pairs during both PM and AM tests (c.f., Dumay, 2016; Muehlroth et al., 2020).

Letter-Shape Discrimination

As a control for the word-pair task, participants were shown 40 pairs of jumbled nonsense words, with instructions to count the number of letters on the screen with a curve in their shape (e.g., S, C, or Q but not T, V, or M; based on Gais et al., 2002). The task was intended to be one that involves similar cognitive engagement (e.g., attentional resources) but without any declarative learning component. This was facilitated by using different lists of nonsense pairs across each phase of the task to avoid explicit or implicit learning effects. The control task was otherwise designed with identical parameters to the learning task (e.g., stimuli of 3-5 characters; same font size, stimulus presentation times, sequence of blocks).

To help preserve participant engagement and motivation, the letter-shape task was introduced not as a "control" task, but as one of "sustained and selective attention". Participants were debriefed about this at the end of the study. Participants were instructed to spend the first two pre-sleep rounds (i.e., the

time when they would be studying word-pairs in the learning task) to simply practice the instruction of counting curved letters. They were encouraged to not worry if the stimuli disappeared before they finished counting letters. During the pre- and post-sleep "testing" periods, participants were given an unrestricted amount of time to count and then verbally report the number of curved letters in each non-word pair. A research assistant recorded their answers on a scoring sheet, however none of the scores from this control task were analyzed for the current study.

Hereafter, data from the recording visit where participants completed the learning/memory task is referred to as the EEGm night, while data from the visit with the control task is referred to as EEGc.

Overnight Sleep Recordings

The first overnight sleep recording consisted of a full polysomnography (PSG). The recording equipment to measure brain, muscle, cardiac, and respiratory activity were identical to those used in Study 1. The second and third recording visits (EEG1 and EEG2) included an 18-channel EEG, but with less ancillary equipment used on the PSG night. EEG recording sensors and placements were identical to those used on Night 2 in Study 1. Physiological signals were collected using Domino equipment and software (bandpass filter 0.2–128 Hz, sampling rate 512 Hz; SomnoMedics, Randersaker, Germany).

EEG Analysis

Sleep records were scored and processed using an in-house software package ("Wonambi"), powered by Python. The EEG pre-processing and analysis steps, including sleep scoring, tagging and removal of artefacts and macro/micro arousals, and detection of oscillatory events, were largely identical to those in Study 1. However, this study also detected both sleep spindles and CFC using a sigma frequency bandwidth that was individually adapted for each participant, to account for individual differences in brain oscillation activity (see below).

SO and Spindle Detection

Automatic detection of slow oscillation (SO) and spindle events was performed using Wonambi, applying the same previously validated detection algorithm (Staresina et al., 2015) used in Study 1. EEG data from Fz was band-pass filtered during a combined N2+N3 sleep stage using artefact-free EEG data

filtered between 0.16–1.25 Hz (zero-phase finite impulse response bandpass filter). Next, candidate SO waves were detected based on zero-crossings in the filtered signals (down-states followed by up-states), as well as event duration and amplitude criteria. Event duration was defined as the time between two successive positive-to-negative zero-crossings within pre-established duration criteria (0.8–2 sec). Event amplitude (trough-to-peak amplitude between two positive-to-negative zero crossings) was determined individually, based on amplitudes that exceeded the 75th percentile of candidate amplitudes for that participant. The resulting SOs fell within a bandwidth of 0.5–1.25 Hz.

Spindle detection in N2 and N3 sleep (based on Mölle et al., 2011) was performed also identical to Study 1, using the same fixed bands (9–13 Hz) as well as individually adapted bands derived from examining spectral peaks using the FOOOF algorithm (Haller et al., 2018). Spectral peaks between 9 and 16 Hz from artefact-free N2 sleep epochs were examined on channel Fz across both experimental nights, and then averaged. If more than one sigma peak was found, the frequency associated with the largest amplitude was selected. As expected, the strongest peaks on this channel were in the slower sigma frequency range. The averaged frontal sigma power peak in YAs was *M* (*SD*) = 11.48 (0.76) Hz, and in OAs was *M* (*SD*) = 10.72 (1.06) Hz; these peaks were significantly different between groups *(t* (30) = 2.333, *p* = .027). A 4-Hz bandwidth was then formed around the mean sigma peaks (i.e., peak +/- 2 Hz), which was used for sigma/spindle detection for each participant. After band-pass filtering Fz data within each frequency band, the root-mean-square (RMS) of the signal was calculated at each data point of the filtered signal using a 0.2 second sliding window and subsequently smoothed. RMS values exceeding thresholds by 1.5 SD for between 0.5 to 3 seconds were identified as spindles. The same procedure was used for adapted fast spindle power on Cz (see Supplemental Results, and Figure S1). Our approach to detecting slow and fast spindle activity on Fz and Cz, respectively, overlaps with Dehnavi et al. (2021).

Event-Locked Cross-Frequency Coupling

Phase-amplitude CFC was analyzed from detected SO events from combined N2+N3 sleep data. See Study 1 Methods for more complete details. The calculation of CFC in this study, especially coupling strength, was modified from Study 1 by examining each detected SO event and deriving a single, grand

average value across all SO events on each study night. From this data, we calculated the Modulation Index (MI; Tort et al., 2010) and measures of preferred coupling phase. To maintain consistency with Study 1, we used a log-transformed MI value (log-MI) for analysis. As in Study 1, instead of focusing on the raw coupling phase we used a transformed measure of coupling phase distance from the SO up-state (referred to as CP), derived in the same way as Study 1. Complementary measures of MI and CP were obtained using fixed and individually adapted bandwidths based on spectral peaks in the sigma range.

Statistical Analyses

Data Screening

Data for the primary CFC (e.g., MI, rel_MI, CP, rel_CP) measures of interest were screened for univariate outliers, and adherence to statistical assumptions of normality and linearity. Univariate outliers were identified by inspecting z-score frequency tables for values +/- 3 SD from the mean, and by inspecting boxplots for extreme values. Normality, skewness/kurtosis, and linearity were screened in the same way as Study 1. There were no concerns about univariate outliers or normality among the log-MI and relative log-MI variables. A univariate outlier was present in a select number of our supplemental measures (i.e., from Cz, or from SO sub-groups), and these were removed from the analysis, as in Study 1. This resulted in 4 data point being removed from our Fz measures (1 for MI and 2 for CP, each from the SO sub-groups, and 1 for a relative change score in MI from SO sub-groups), and 2 data points removed from our Cz measures (both for relative change in CP, one from all SO events and another from SO sub-groups). Square-root transformations meaningfully improved or fully corrected remaining distributional deviations in several of our primary CP variables. Similar transformations were not deemed warranted for measures of MI, or for measures of relative change used in regression analyses.

Between-Group and Across-Night Comparisons.

Measures of MI and CP were compared across (YA and OA) groups and between control (EEGc) and learning (EEGm) nights to examine any significant differences between conditions. Measures were examined using a 2 (Night) X 2 (Group) within- and between-subjects repeated measures ANCOVA, with recording night (EEGc vs. EEGm) as a repeated measures factor. To maintain consistency with Study 1

we included age and sleep apnea severity as covariates in these analyses; covariates were mean-centered to each group separately, to capture variability in these measures within each age-group category. We also quantified the stability of MI and CP between the two experimental nights using Pearson's correlations. Supplemental analyses (presented after the Discussion section) show similar ANCOVA models conducted on CFC data from Cz (using fast-spindle activity) and from SO sub-groups.

Associations between MI and CP with Word-Pair Memory.

Coupling measures were examined for relations with memory using a measure of relative change (increase vs. decrease) between nights: [(learning task/EEGm night) – (control task/EEGc night)]; these measures are referred to as relative MI (rel_MI) and relative CP (rel_CP). These analyses helped elucidate if changes in CFC during sleep after the learning (vs. control) task can predict word-pair overnight memory consolidation across the two groups. CFC measures (rel_MI, rel_CP) from all-night N2+N3 sleep were separately entered into distinct hierarchical regression models: In Step 1, models examined the influence on memory by participant age and sleep apnea severity. In Step 2, the CFC measure of interest was added to examine cumulative effects on predicting word-pair recall performance. The R^2-change and *F*-scores were examined alongside standardized regression coefficients to determine the effects of CFC in component bandwidths in predicting word-pair overnight memory consolidation.

Correction for Multiple Comparisons.

Critical *p*-values in this study were adjusted similarly to Study 1. A Bonferroni method was used to account for the number of analyses performed using our primary measures (MI, CP). Given our examination of group-by-night effects and associations with memory, as well as analyses between fixed- and adapted-band conditions, this study conducts a total of 8 primary analyses; in turn, our critical alpha value was adjusted to (.05 / 8 = 0.006). In treating each group as an independent sample, the same adjusted *p*-value was applied to both groups.

Results

Sample Characteristics and Participant Screening

Participant demographics and results of the preliminary screening assessments are presented in Table 1. Young adult (YA) participants (*M* [*SD*] age = 24.50 [3.31] years), were balanced in terms of sex (56.3% female) and were mostly right-handed (75%). Older adult (OA) participants (*M* [*SD*] age = 67.44 [6.81] years), were modestly balanced in terms of sex (66.7% female), and all (100%) were right-handed. In both groups, 75% of participants were primarily English-speaking. Descriptive statistics and group comparisons for parameters from the first (PSG) sleep recording and from at-home sleep diary and wrist actigraphy (Actiwatch) monitoring are presented in Supplemental Tables S1 and S2, respectively.

Word-Pair Associates Task

Participants completed pre-sleep (PM) and post-sleep (AM) recall testing on their EEGm visit. YA participants recalled an average of 36.94 (*SD* = 2.49; range = 33–40) words on the PM cued-recall test, and of 36.75 (*SD* = 3.0; range = 33–40) words on the AM test. OA participants recalled an average of 33.25 (*SD* = 5.50; range = 17–40) words on the PM test, and of 31.19 (*SD* = 6.20; range = 14–40) words on the AM test. The difference in recall performance between groups was significant during both PM (t (30) = 2.45, p = .021) and AM (t (30) = 3.23, p = .003) recall tests.

The overnight (pre-sleep to post-sleep) absolute change in word-pair recall in the YA group ranged from forgetting 2 word-pairs to remembering 1 additional word-pair (*M* [*SD*] = -0.19 [0.98]; *Med* = 0; *Mode* = 0), and in the OA group ranged from forgetting 5 word-pairs to recalling the same number of words as in the PM test (i.e., no gains; *M* [*SD*] = -1.61 [0.10]; *Med* = -2; *Mode* = -3). The Overnight Consolidation score, reflecting the number of correct word-pair responses involving the *same* word-pairs between PM and AM tests, ranged from 33 to 40 in YAs (*M* [*SD*] = 36.44 (2.94)) and from 14 to 40 in OAs (*M* [*SD*] = 29.88 (6.44); t (30) = 3.71, p = .001).

Sleep Parameters

Sleep Architecture

Presented in Table 2 are descriptive statistics and group comparisons of sleep parameters for each of the control (EEGc) and learning task (EEGm) nights. A 2 (Group) x 2 (Night) ANCOVA, controlling for age and sleep apnea severity, revealed that YAs achieved significantly higher sleep efficiency (F(1,

28) = 11.955, p = .002) and percent of N3 sleep (F(1, 28) = 15.034, p = .001) compared to the OA group. By contrast, OAs achieved significantly higher percent of N1 sleep (F(1, 28) = 6.921, p = .014) and N2 sleep (F(1, 28) = 11.901, p = .002), a longer duration of wake after sleep onset (F(1, 28) = 14.826, p = .001), and a higher sleep fragmentation index (F(1, 28) = 16.257, p < .001). There were no significant differences between nights in any parameter, and no Group x Night interactions.

Discrete Oscillatory Events

Table 3 presents descriptive statistics and comparisons for detected slow oscillation (SO) events. YAs evidenced significantly higher SO peak-to-peak amplitude (F(1, 28) = 34.327, p < .001) and SO energy (F(1, 28) = 18.204, p < .001) versus the OA group. Intriguingly, both measures also evidenced a significant decline after the learning task compared to the control task (peak-to-peak: F(1, 28) = 8.401, p = .007; energy: F(1, 28) = 16.257, p = .011). No other effects were observed, and there were no significant Group x Night interactions.

Presented in Table 4 are descriptive statistics and comparisons for detected (Fz) sleep spindles using both a fixed frequency bandwidth (9–13 Hz; upper panel) and individually adapted bands (lower panel). Regarding fixed bands, the YA group evidenced significantly higher sleep spindle duration (F(1, 28) = 3.422, p = .027), peak-to-peak amplitude (F(1, 28) = 29.456, p < .001), energy (F(1, 28) = 8.217, p = .008), and peak energy frequency (F(1, 28) = 4.347, p = .046) versus the OA group. The number of detected spindles also appeared to increase in both groups from the control to the learning task night (F(1, 28) = 4.627, p = .040). Regarding adapted bands, every measured spindle parameter was higher in the YA group (F-range = 5.029-21.515, all ps < .033). However, there were no night effects for adapted-band spindles, and no Group X Night interactions in either bandwidth condition.

Specific Aim 1: SO – σ CFC and Relations with Pre-Sleep Learning in Young and Older Adults

Presented in Table 5 are descriptive statistics from both groups of our measures of MI and CP, derived from all detected SO events on each study night, and in both fixed- (9–13 Hz) and adapted-band conditions. Coupling dynamics (sigma amplitude increases, coupling phase) from all SO events are plotted in Figure 2. Overall, fixed-band analyses are consistent with previous reports in suggesting that

increases in slow sigma power amplitude occur mainly in the up-to-down-state transition phase; however, the mean amplitude increase and preferred coupling phase both appear closer to the down-state in YAs, while in OAs the peak occurs earlier in time and closer to the up-state. Adapted-band analyses suggest a similar pattern, except that amplitude modulations in YAs were more subtle versus OAs, and the raw coupling phases in both groups appeared more varied (i.e., less precise) relative to fixed-bands.

Modulation Index (MI)

A 2 (Group) x 2 (Night) ANCOVA (Table 6; Figure 3A and 3C), controlling for age and sleep apnea, revealed a trend for greater MI in YAs versus OAs in the fixed-band analysis ($F(1, 28) = 5.148$, $p = .031$, Partial $\eta^2 = .155$; does not survive p-value correction). No other effects for MI were observed in either bandwidth condition and there were no Group x Night interactions.

Coupling Phase Distance from the Up-State (CP)

Also shown in Table 6 are results of a similar 2 (Group) x 2 (Night) ANCOVA examining our transformed measure of CP (see also Figure 3B and 3D). In the fixed-band condition, a significant effect of group ($F(1, 28) = 16.151$, $p < .001$, Partial $\eta^2 = .366$) suggested that CP in the OA group was significantly closer to the up-state compared to the YA group, whose coupling phase was locked later in the up-to-down-state transition, and closer to the down-state. By contrast, there were no group effects in measures of CP with adapted bands beyond a trend night effect ($F(1, 28) = 4.409$, $p = .045$, Partial $\eta^2 = .136$; does not survive p-value correction), which suggests that CP shifted further away from the up-state after learning, and primarily in the YA group. No other effects for CP were observed in either bandwidth condition and there were no Group x Night interactions.

Specific Aim 2: SO – σ CFC and its Relations with Declarative/Episodic Memory.

Modulation Index (MI)

Measures of relative change between nights in SO – σ MI, derived using all SO events and across fixed- and adapted-band conditions, were examined in separate hierarchical multiple regression models for their ability to predict overnight memory consolidation, controlling for age and sleep apnea severity

(Table 7). Relative change in MI (rel_MI) was not associated with memory consolidation scores in either group or bandwidth condition (all *p*s > .221; see Figure 4A and 4C).

Coupling Phase Distance from the Up-State (CP)

Also shown in Table 7 are results of similar regression models for measures of rel_CP. Like above, no significant associations with memory were observed in either group or bandwidth condition (see Figure 4B and 4D).

Specific Aim 3: Interactions Between MI and CP and Relations with Memory

Results from our exploratory interaction models are presented in Table 8. A model containing SO – σ MI and CP from the EEGm night, and their interaction, did not significantly predict memory consolidation in either group or bandwidth condition (*F*-range = 0.138-1.148, all *ps* >.396). As there were no significant interactive effects between MI and CP, no follow-up analyses were performed.

Taken together, beyond a trend effect, MI was largely equivalent between YA and OA groups in both band-pair conditions. By contrast, CP was significantly further away from the up-state in YAs, but only when measured using fixed bands. Similarly, and except for a trend effect in the adapted-bands condition for YAs, CP was largely stable across nights in both age groups. Moreover, individual (relative) change in MI or in CP was not predictive of overnight memory consolidation, and there were no interactive effects of MI and CP on the learning night in predicting memory consolidation.

Discussion

The overarching aim of this study was to examine SO – σ CFC during NREM sleep and relations with overnight declarative memory consolidation in the context of ageing. First, this study compared measures of coupling strength (MI) and coupling phase distance from the SO up-state (CP) between healthy younger and older adults and across study nights. Contrary to expectation, there were no significant differences in MI between groups when measuring from all SO events, beyond a trend-level difference for greater fixed-band MI in YAs. Conversely, and in partial support of our hypothesis, a significant age-group difference in CP on Fz verified that CP with slow spindle power in OAs was closer to the up-state and CP in the YAs was closer to the down-state. Like the MI, differences in CP between

groups were only found in the fixed-band condition. The hypothesis that learning alters SO – σ CFC was partially supported, as a trend main effect of night was seen in YAs, suggesting that CP in this group shifted even closer to the down-state after learning. Second, this study examined if measures of SO – σ CFC are related to memory consolidation scores on our word-pair associates task. The hypothesis that greater SO – σ MI or CP closer to the up-state would be associated with memory was not supported, as there were no significant associations with memory consolidation scores in either group or bandwidth condition on Fz. Third, this study attempted to replicate the exploratory interaction described in Study 1 by repeating the interaction models in this new sample of OAs and contrasting with results from the YA group. Contrary to Study 1, no interactive effects of MI and CP in predicting memory scores were found. Taken together, this study provides evidence for age-group differences in coupling more generally, and in particular with our transformed measure of CP from Fz. These results corroborate earlier findings of age-group differences in the SO phase of maximal spindle power. However, we did not obtain strong evidence for associations between CFC and learning or overnight memory consolidation in either group.

SO – σ Phase-Amplitude Dynamics Across Groups

Interesting group differences were evident in the phase-amplitude histograms and circular plots across the different analyses. From all SO events, increases in slow spindle/sigma power were time-locked with the up-to-down-state transition phase and occurred closer to the down-state in YAs but closer to the up-state in OAs. Circular (polar) plots, reflecting the raw coupling phase, are concordant with the mean-amplitude plots, and the patterns are consistent between the control and learning nights in both groups. This coupling pattern with slow spindle power is consistent with previous reports (Helfrich et al., 2018; Ladenbauer et al., 2021). Fz coupling dynamics were largely consistent between fixed- and adapted-band conditions, except that amplitude modulations were more subtle in the YA group compared to fixed bands and compared to OAs. Findings from Fz can be contrasted with results from supplemental analyses on Cz, where sigma power was often maximum before or during the up-state in YAs in both bandwidth conditions but peaked earlier in the down-to-up rising SO phase in OAs, which is also consistent with previous reports (Helfrich et al., 2018; Ladenbauer et al., 2021; Muehlroth et al., 2019).

One noteworthy observation from our supplemental analyses with SO sub-groups was of an opposing pattern of coupling dynamics between Fz and Cz. Specifically, phase-amplitude dynamics on both Fz and Cz followed the same patterns that were seen among analyses from all SO events, however the amplitude increases among SO(+) events on Fz appeared larger and more clearly defined compared to Cz, and compared to the SO(-) condition, while amplitude increases among SO(-) events on Cz appeared larger and more clearly defined compared to Fz, and compared to the SO(+) condition. Although curious, this result can be contextualized by noting the relatively larger amplitude and longer duration of sleep spindles that were detected on Fz compared to Cz (compare Table 4 and Table S4), both of which could have reasonably impacted coupling with sigma power when SOs and spindles were examined together. Accordingly, and as reflected by our circular statistics (Supplemental Results), the raw coupling phase among SO(+) events on Fz was much more varied compared to other measures, which may also signal the differences in timing between the two sleep events across both channels. These results provide additional support for arguments that spindles and sigma power are distinct measures with unique functional properties, and that the presence of spindles may alter sigma activity and its relation with the SO phase.

Between-Group and Across-Night Differences in SO – σ CFC

Age-group differences in SO – σ coupling strength were not observed in our main analyses with Fz, except for a trend-level difference with YAs showing greater fixed-band MI. However, MI was significantly greater in YAs on Fz in our supplemental analyses with isolated SO events not joined with a spindle (SO(-) – σ). No group differences were found for any measure of MI from Cz (see Supplemental Results). Conversely to MI, the groups differed in SO – σ CP from Fz, but only when using fixed bands, with CP in YAs being closer to the down-state compared to OAs. Analyses with SO sub-groups suggested that this effect is mostly driven by coupling dynamics among SO(-) events. Other supplemental analyses with CP (from Cz) revealed a strong trend-level differences for SO(+) – σ CP, with the peak in YAs being closer to and just before the up-state versus OAs, whose CP was earlier in the down-to-up-state transition. These findings support previous observations of ageing-related declines in SO – σ CFC (c.f., Djonlagic et al., 2021; Helfrich et al., 2018; Muehlroth et al., 2019), where coupling dynamics may become weaker or

less precise with greater age. The results also suggest that age differences in CFC may depend on the presence or absence of a detectable sleep spindle, with greater differences seen when a spindle is absent.

SO – σ coupling strength (MI) and CP were both stable on average across the two experimental nights, as reflected by a lack of significant between-night differences in either measure across both groups. One exception in our main analysis with YAs was for a trend increase in adapted-band CP, reflecting a shift further away from the up-state after learning. Similarly, we did not see any night main effects in any of our supplemental analyses with MI or CP, or between-night differences in raw coupling phase. CFC measures remained stable across the two experimental nights despite the coinciding decline in activity among the detected SOs (peak-to-peak amplitude, energy) that were used to derive the measures. Overall, the lack of difference in MI or CP across the two experimental nights is consistent with Study 1, and with others (Bastian et al., 2022; Cox et al., 2018), and adds to a mixed literature regarding the association between SO – σ CFC and learning/memory.

These results do not support a hypothesis that SO – σ CFC during NREM sleep is modulated at the group-level by a pre-sleep learning experience; instead, results are more in-line with a hypothesis that SO – σ CFC reflects a stable, individual difference in brain activity, and perhaps across the lifespan. However, given the age-group differences in coupling that have been noted previously (Helfrich et al., 2018; Ladenbauer et al., 2021; Muehlroth et al., 2019) and observed here, it is likely that any changes/declines in CFC across the lifespan occur gradually, and thus appear stable in younger and older groups when examined only through a cross-sectional lens. The factors that influence the rate and magnitude of such lifespan changes in CFC remain unclear, as there is a noteworthy lack of longitudinal studies to examine within-subject change in SO – σ CFC across longer time intervals.

SO – σ CFC and Sleep-Associated Declarative Memory Consolidation

The activity of TC sleep spindles is known to facilitate long-term potentiation and overnight memory consolidation (Fernandez & Lüthi, 2020; Gais et al., 2002; see also Kumral et al., 2022 for a meta-analysis). Spindle-mediated learning processes are largely attributed to thalamic-reticular burst firing and a spindle-induced influx of Ca^{2+} ions into pyramidal cells across distributed cortical regions

that, together, facilitate the growth of dendritic spines and synaptic potentiation (Fernandez & Lüthi, 2020; Ulrich, 2016). Evidence is similarly growing for a role of SO – σ CFC in overnight memory consolidation, provided through observational research and experimental studies that use external interventions (e.g., electrical stimulation, e.g., Dehnavi et al., 2021; Ladenbauer et al., 2017) or sensory cueing (e.g., targeted memory reactivation; Bar et al., 2020; Göldi et al., 2019; rocking stimulation, Perrault et al., 2019). Chiefly, and in-line with the "active systems model" of memory consolidation (e.g., Geva-Sagiv & Nir, 2019; Klinzing et al., 2019; Muehlroth et al., 2020), the precise SO-spindle timing and concurrent synchrony between spindles and faster HC ripples (e.g., > 80 Hz) is thought to provide a time-window for the optimal synchronization of distinct neural (re)activation patterns. However, empirical support for this model is still emerging, given the limited studies available to examine SO-spindle-ripple CFC in the context of both memory performance and ageing.

The current study examined if SO – σ CFC can predict overnight memory consolidation across both groups, using a measure of relative increase or decrease after learning in coupling strength (rel_MI) or coupling phase distance from the up-state (rel_CP) (same as Study 1). Unlike Study 1, the current analyses found limited associations between SO – σ CFC and memory consolidation in either group. Only one trend-level correlation with memory was seen in our supplemental analyses with SO(+) – σ (*a*) raw coupling phase on Cz in the OA group, suggesting that a coupling phase closer to the pre-up-state was associated with better memory consolidation, while memory scores declined when coupling phases landed earlier in the down-to-up-state transition or after the up-state. This trend finding is consistent with previous reports of CFC and declarative memory in young adults (e.g., Mikutta et al., 2019), and is novel in that the result was specific to coupling on SO-spindle complexes and only in the OA group.

In general, this study did not find strong evidence that SO – σ CFC predicts overnight memory consolidation, which was opposite to expectation. However, supplemental analyses revealed some trend-level effects with SO power spectral density (PSD) in YAs, and SO and (fixed) sigma PSD in OAs. The lack of associations between better memory and *coupled* brain activity in our younger sample could be due to the task itself. Indeed, the YAs were mostly university students and may have found our 40 word-

pair task too easy, as evidenced by a slight ceiling effect in their performance (e.g., 56% recalling ≥35 correct word-pairs on AM testing); however, the same task appeared sufficiently challenging for the OA group (e.g., 25% recalling ≥35 correct word-pairs on AM testing). Importantly, Mikutta et al. (2019) found a positive correlation between SO – σ raw coupling phase and declarative memory performance among 20 YAs exposed to a 15-item single-word list. Thus, the potential relevance of learning load on SO – σ CFC requires further examination to determine if the type of test or number of tested items is relevant for any associations between coupling and memory.

SO – σ CFC and Ageing

The present study adds to a currently limited pool of knowledge about SO – σ CFC in ageing and memory. Analysis of coupling dynamics corroborate previous reports of faster spindle power peaking earlier in the rising SO phase in OAs but often just before or during the up-state in YAs, and of slower spindle power peaking during the up-to-down-state transition, and closer to the down-state in YAs. Slow-spindle coupling phase distance from the up-state on Fz was significantly different between the YA and OA groups, and was perhaps driven by measures from isolated SO events that are not joined with a spindle (SO(-); Supplemental Results). The significant difference between groups in CP only on Fz could reflect that age-related changes in frontal regions are perhaps more dramatic in healthy seniors compared to changes or age-group differences across more central or posterior brain regions. More generally, in both fast and slow frequency conditions the OAs evidenced a maximal peak that was earlier in the SO phase relative to YAs. This earlier timing of coupled brain activity could be a natural consequence of ageing, and perhaps related to one or both of a) impaired SO-triggered spindles that present too early across the SO phase, and b) more blunted and slower SOs that cannot properly group spindle activity like in YAs. In either case, the timing of SO and both slow and fast spindle activity appears to "de-couple" with greater age, which may reflect ageing-related structural changes (e.g., reduced grey matter volume) in both medial pre-frontal and thalamic brain regions (Helfrich et al., 2018; Muehlroth et al., 2019).

To our knowledge, only one study has directly compared SO – σ CFC and memory across groups of healthy younger adults, healthy older adults, and seniors with MCI (Ladenbauer et al., 2021). This nap

study demonstrated similar coupling patterns in YAs and OAs as observed here, while also noting an even more attenuated coupling pattern in OAs with MCI, but reporting no differences in coupling strength between groups or strong associations between CFC and word-pair memory. Considering these results alongside the current study, perhaps the ageing-related changes in coupling that have been observed have a stronger negative impact on tests of recognition (vs. recall) memory recall; indeed, the ageing-related effects on memory reported by both Helfrich et al. (2018) and Muehlroth et al. (2019) were from studies that emphasized tests of recognition memory.

Study Limitations and Strengths

This study has 3 main limitations. First, this study has a generally small sample size of only 16 participants in each group, making it possible that our analyses were too underpowered to detect more statistically meaningful effects. Given the number of trends we observed, the effects of pre-sleep learning and of ageing on SO – σ CFC may have been clearer with a larger sample. Second, and as mentioned above, our 40-item word-pair task may not have been challenging enough for the YA group to show the predicted associations between CFC and performance. As noted by others (Muehlroth & Werkle-Bergner, 2020; Muehlroth, Rasch, & Werkle-Bergner, 2020), it is important to consider the "age-fairness" of a study design when studying older adults. While the test itself appeared suitable for our OA group, a more challenging test for YAs (e.g., fewer learning trials or more items to memorize), may have enhanced the associations between coupling and memory (e.g., more within-group variability in task performance). Third, while the current 3-night protocol allowed participants to acclimate to the lab and equipment before the experimental procedures began, this protocol is still limited by drawing comparisons with only one other condition (non-learning control task), which precludes inferences about how CFC might differ after learning versus a control task as compared to a no-task baseline (following acclimation); this would require a minimum 4-night protocol, where one of the three experimental nights contains no task at all.

Noted strengths of this study overlap with strengths listed for Study 1, with four additional points worth mentioning. First, the 3-night protocol used here allowed participants to acclimate to lab conditions and recording equipment before starting the experimental procedures. Second, including a non-learning

control task allowed for stronger inferences about the effects of learning on SO – σ CFC, over and above the potential influences of pre-sleep cognitive engagement. Third, each of our primary and supplementary analyses were conducted using complementary datasets of SO – σ CFC to allow for comparisons between measures derived using fixed and individually adapted sigma bands, and between SO sub-groups; this highlighted the difference in outcome when CFC measures were derived in consideration of individual differences in brain activity, compared to fixed-band measures that treated all participants the same. Finally, our inclusion of participants with no more than mild sleep apnea is a strength, given that it allowed for better methodological control of our sample; however, it is possible that doing so also limited the generalisability of results obtained from the OA group. It is crucial that researchers objectively screen for sleep apnea, and to report this in their studies to help better contextualize their sample; screening and reporting of sleep apnea severity is inconsistent across the sleep literature, and particularly among studies with young adults where sleep apnea is less-often suspected but could still be present.

Conclusion

In sum, this study builds on the currently limited empirical literature examining SO – σ CFC and memory in ageing. Using a within- and between-subjects design, this study found evidence for age-group differences in SO – σ CFC in the slow spindle power band, and specifically related to measures of coupling phase distance from the up-state. Analyses across nights and in relation to word-pair memory performance did not reveal any significant associations between coupling and memory. However, additional analyses revealed that stronger or clearer associations of coupling with ageing and memory may be revealed when measures are examined across SO sub-groups (SO(+) and SO(-) events), and when coupling measures are derived using a fixed sigma power bandwidth for all subjects (vs. individually adapted frequency bands). Together, findings from this study suggest that SO – σ coupling dynamics may indeed shift across the lifespan, but also that the association between SO – σ CFC and learning/memory remains unclear given the limited associations with performance found in either YA or OA group.

Supplementary Material

Supplementary Methods

Detection of Co-Occurring SO-Spindle Complexes

The occurrence of overlap between detected SO and spindle events was obtained using a specialized script function. This script function and its parameters (e.g., separating events into SO(+) and SO(-) events, minimum 25% overlap between the two events at any point in the SO phase) was identical to Study 1, except that now this script measured the phase position and amplitude changes in the overlapping sleep spindles themselves, instead of relying on just the surrounding sigma frequency power. These overlapping (SO(+)) and non-overlapping (SO(-)) events were then examined for SO – σ CFC and associations with learning and memory as described above.

Raw SO – σ Coupling Phase

Supplemental analyses present descriptive statistics and between-night comparisons for raw coupling phase (circular metric), as well as circular-linear correlations with memory in each group. Differences between nights were tested like in Study 1, using a Watson-Williams test with permutation shuffling (10,000 permutations; Watson & Williams, 1956; see also Berens, 2009), and after verifying the presence of a preferred coupling direction (vs. uniform distribution) on both nights (Fisher, 1995). Circular-linear correlations were examined in both groups and across both (Fz and Cz) channels.

Power Spectral Analysis

Power spectral density (PSD) analysis was also performed in the same fashion as Study 1, and applied to both YA and OA groups. The primary exception is that PSD analyses in this study also included data from sigma power derived using individually adapted frequency bands. See Study 1 Supplemental Methods for more complete details of our PSD analysis.

Supplementary Results

S.1. Results of PSG Screening and At-Home Sleep Monitoring

The results from participants' initial PSG screening night are presented in Table S1. Similar to the two experimental nights (see main paper), the YA group achieved greater sleep efficiency (t (30) = 2.833,

p = .008) and less percent of N1 sleep (t (30) = -2.53, p = .017) compared to the OA group. Unsurprisingly, OAs evidenced higher sleep apnea severity compared to YAs (t (30) = 2.833, p = .008).

Table S2 presents results from the at-home sleep monitoring using self-reported sleep diaries and Actigraph monitoring. In both measures, the YA group evidenced significantly lower duration of wake after sleep onset (sleep diary: t (30) = -3.44, p = .003; Actiwatch: t (27) = -2.42, p = .033) and later wake up time versus the OA group (sleep diary: t (25) = 2.14, p = .042; Actiwatch: t (27) = 4.07, p < .001). In just the sleep diary, the YAs evidenced significantly longer total sleep time (t (30) = 2.84, p = .008) and greater overall sleep efficiency (t (30) = 4.09, p < .001).

S.2. Descriptive Statistics and Comparisons of Event-Detected SOs and Spindles from Cz

Table S3 presents descriptive statistics and comparisons for slow oscillation (SO) events detected on channel Cz. The pattern of results was the same as on Fz, with YAs showing greater SO peak-to-peak amplitude (F(1, 28) = 35.356, p < .001) and SO energy (F(1, 28) = 24.121, p < .001) versus the OA group, and a significant decline in both measures after the learning (vs. control) task (peak-to-peak: F(1, 28) = 15.568, p < .001; energy: F(1, 28) = 17.183, p < .001). Unlike Fz, there was a Group X Night interaction for SO energy on Cz (F(1, 28) = 7.868, p = .009), suggesting that the decrease in energy on the learning task night was greater in the YA group. No other main effects or interactions were observed.

Presented in Table S4 are descriptive statistics and comparisons for detected (Cz) sleep spindles using both a fixed frequency bandwidth (12–16 Hz; upper panel) and individually adapted bands (lower panel). In both bandwidth conditions, the YA group evidenced significantly higher number, density, duration, peak-to-peak amplitude, and energy compared to the OA group (F-range = 7.289-31.611, all ps < .012). As well, there were increases seen during sleep after the learning task in fast spindle number, density, and especially peak-to-peak amplitude (fixed bands: F(1, 28) = 12.929, p = .001; adapted bands: F(1, 28) = 11.470, p = .002). However, there were no Group x Night interactions.

S.3. SO – σ CFC on Cz Between Nights and Groups, and Relations with Memory Consolidation

Presented in Table S5 are descriptive statistics for our measures of MI and CP, derived from all detected SO events on Cz from each study night, and in both fixed- (12–16 Hz) and adapted-band

conditions. Phase-amplitude dynamics for measures from all SO events on Cz are plotted in Figure S2. In contrast to the main analyses above with slow sigma power on Fz, fast sigma power on Cz displayed the expected relationship with the SO up-state, such that spindle activity peaked during or just after the up-state in YAs but peaked before the up-state in OAs. Results were similar between analyses with fixed and adapted bands, which is not surprising given that the sigma peaks in both conditions were very similar.

Modulation Index (MI)

A 2 (Group) x 2 (Night) ANCOVA (Table S6), controlling for age and sleep apnea severity, revealed no differences in MI between groups or across nights in either bandwidth condition, and no Group x Night interactions (see Figure S3A and S3C). As well, MI on channel Cz was not associated with memory consolidation in either YA or OA group (Table S7).

Coupling Phase Distance from the Up-State (CP)

Also shown in Table S6 are results of a similar 2 (Group) x 2 (Night) ANCOVA examining our transformed measure of CP (see Figure S3B and S3D). As with the MI, there were no main effects of group or of night, and no interactions for this measure on Cz. Similarly, there were no associations found between CP and memory consolidation (Table S7).

MI x CP Interaction

Lastly, we repeated our exploratory interaction model using measures of fixed-band and adapted-band CFC measured from Channel Cz (Table S8). A model containing SO – σ MI and CP from the EEGm night, and their interaction, did not significantly predict memory consolidation in either group or bandwidth condition (F-range = 0.219-1.004, all ps >.463). As there were no significant interactive effects between MI and CP, no follow-up analyses were performed.

S.4. Descriptive Statistics and Comparisons of SO(+) and SO(-) Events

Presented in Table S9 are descriptive statistics for the raw SO(+) and SO(-) events, and associated F1 ratios, using data derived from the spindle detections performed with fixed bands. Table S10 presents the same measures derived from the spindle detections with adapted bands. Unsurprisingly, there were fewer SO(+) events than SO(-) events in both groups, however there were no between-group

differences in the number or density of either SO(+) or SO(-) events across both channels and bandwidth conditions. SO and spindle co-occurrence (via F1) was generally low, but still highly correlated across both nights in both groups (YA: [Fz: *r*-range = 0.724-0.778, $p \leq 0.002$; Cz: *r*-range = 0.901-0.911, $p \leq 0.001$], OA: [Fz: *r*-range = 0.846-0.878, $p \leq 0.001$; Cz: *r*-range = 0.814-0.846, $p \leq 0.001$]*).*

S.5. Analyses of SO – σ CFC on SO sub-groups on Fz and Cz

Presented in Table S11 are descriptive statistics for our measures of MI and CP, derived from sub-groups of SO(+) and SO(-) events, on both Fz and Cz channels and in both bandwidth conditions. Phase-amplitude dynamics across SO sub-groups are plotted and described in Figures S4 (Fz, SO(+)), S5 (Fz, SO(-)), S6 (Cz, SO(+)), and S7 (Cz, SO(-)).

S.5.1.* SO – σ *CFC on SO Sub-Groups Between Study Groups and Across Nights

Modulation Index (MI). Results of a 2 (Group) x 2 (Night) ANCOVA for SO(+) and SO(-) MI in both fixed- and adapted-band conditions are presented for Fz in Table S12, and for Cz in Table S13. On Fz, a significant effect of group was found for SO(-) – σ (*f*) MI, such that coupling strength was greater in the YA group ($F(1, 28) = 13.641$, $p = .001$, Partial $\eta^2 = .336$). A similar trend was found for SO(-) – σ (*a*) MI ($F(1, 28) = 5.123$, $p = .032$, Partial $\eta^2 = .155$). No main effects of group or night were found on channel Cz, and there were no Group x Night interactions on either channel.

Coupling Phase Distance from the Up-State (CP). Results of a 2 (Group) x 2 (Night) ANCOVA for SO(+) and SO(-) CP in both fixed- and adapted-band conditions are presented for Fz in Table S14, and for Cz in Table S15. On Fz, but only in fixed bands, there was a trend for greater CP in the YA group for SO(+) – σ ($F(1, 28) = 4.567$, $p = .041$, Partial $\eta^2 = .140$), and significantly greater CP in YAs for SO(-) – σ ($F(1, 28) = 26.466$, $p < .001$, Partial $\eta^2 = .495$), both results indicating that the coupling phase of slow spindle power on these events was further away from the up-state and closer to the down-state in YAs versus OAs. With measures from Cz, SO(+) – σ (*f*) CP was lower in the YA group ($F(1, 28) = 8.385$, $p = .007$, Partial $\eta^2 = .230$), and there was a trend for lower SO(+) – σ (*a*) CP in YAs ($F(1, 28) = 6.137$, $p = .020$, Partial $\eta^2 = .180$), but no main effects of group for either SO(-) – σ CP measure. There were no Group x Night interactions on either channel.

S.5.2. SO – σ *CFC on SO Sub-Groups and Associations with Overnight Memory Consolidation*

Modulation Index (MI). Measures of relative change between nights in SO(+) – σ and SO(-) – σ MI (rel_MI), across both channels and both fixed- and adapted-band conditions, were examined in separate hierarchical multiple regression models for their prediction of overnight memory consolidation, controlling for age and sleep apnea severity (Table S16). Rel_MI was not associated with memory consolidation scores in either group, channel, or bandwidth condition (all *p*s ≥ .238).

Coupling Phase Distance from the Up-State (CP). Presented in Table S17 are results of similar regression models for measures of rel_CP from the SO sub-group events. Like above, no significant associations with memory were observed in either group or bandwidth condition (all *p*s > .05).

S.6. Analysis of SO – σ Raw Coupling Phase

S.6.1. SO – σ Raw Coupling Phase Between Nights and Groups

All SO Events. We next looked for effects of learning on the preferred SO – σ raw coupling phase (in radians, 0–360°) using circular statistics (Table S18; see also Figure 2 (Fz) and Figure S2 (Cz)). Rayleigh tests confirmed a unimodal circular distribution for measures from both channels (all *p*s < .003), however there were no differences in raw coupling phase between nights in either group (all $F_{W\text{-}W}$ (Fz) ≤ 0.096, all $p \geq .293$; all $F_{W\text{-}W}$ (Cz) ≤ 0.161, all $p \geq .339$).

SO+Spindle (SO(+)) and SO-Spindle (SO(-)) Events. Raw coupling phase was then examined for each sub-group of SO(+) and SO(-) events in both bandwidth conditions (see Figures S4-S7, with circular statistics in Table S19. Phase-amplitude dynamics are plotted and described in Figures S4-S7. Chiefly, Figure S4 showed an anomalous pattern, where coupling phases in SO(+) – σ CFC on Fz were much more dispersed and varied across the SO phase, and occasionally falling after the down-state, despite the amplitude modulations still falling within the expected SO phase bins. Accordingly, Rayleigh tests confirmed a unimodal circular distribution across all variables and conditions, except for SO(+) – σ (*f*) and SO(+) – σ (*a*) on Fz in both groups. Of the remaining variables, there were no significant differences in raw coupling phase between nights in either group ($F_{W\text{-}W\ range}$ = 0.005-0.749, all *p*s ≥ .332).

S.6.2. SO – σ Raw Coupling Phase and Correlations with Memory Consolidation

All SO Events. Presented in Table S20 are SO – σ circular-linear correlations with SO – σ raw coupling phase word-pair overnight memory consolidation in both groups, channels, and band-pair conditions. For measures derived from all SO events, no significant correlations were found between any raw coupling phase measure and memory consolidation on either channel.

SO+Spindle (SO(+)) and SO-Spindle (SO(-)) Events. Table S20 also shows circular-linear correlations between raw coupling phase with word-pair memory consolidation, derived from SO(+) and SO(-) events across both groups, channels, and band-pair conditions. Trend-level correlations with memory consolidation were found in the OA group for SO(+) – σ (*f*) ($r = 0.612$, $p = .050$) and SO(+) – σ (*a*) raw coupling phase on Cz ($r = 0.724$, $p = .015$).

S.7. Power Spectral Density in Relation to Learning and Memory Consolidation

Lastly, presented in Table S21 are descriptive statistics of normalized PSD values from NREM sleep in each bandwidth (SO, sigma [fixed and adapted]), with between-group and across-night comparisons shown in Table S22. A trend group effect was found for fixed sigma power on Fz, whereby YAs evidenced greater power in this channel than OAs. No other main effects were found, and only one trend Group x Night interaction was observed for adapted sigma power on Fz, suggesting that an increase in power from the control to the learning night was evident only in the YA group.

Presented in Table S23 are regression models like those above, with relative change between nights in PSD as a predictor of memory consolidation. Trend-level predictions of better memory consolidation were found in YAs for a relative increase in SO power after learning on both Fz *(*F (3, 12) = 2.072, $\Delta R^2 = 0.341$, *B(SE)* = 11.589 (4.652), $\beta = .586$, $p = .028$*)* and Cz *(*F (3, 12) = 2.725, $\Delta R^2 = 0.405$, *B(SE)* = 12.241 (4.284), $\beta = .656$, $p = .014$*).* As well, trend effects were seen on Cz from measures in the learning task night in the OA group for greater SO power *(*F (3, 12) = 3.711, $\Delta R^2 = 0.244$, *B(SE)* = 7.206 (3.036), $\beta = .543$, $p = .035$*)* and fixed (but not adapted) sigma power *(*F (3, 12) = 4.804, $\Delta R^2 = 0.308$, *B(SE)* = 2.225 (0.780), $\beta = .685$, $p = .015$*).*

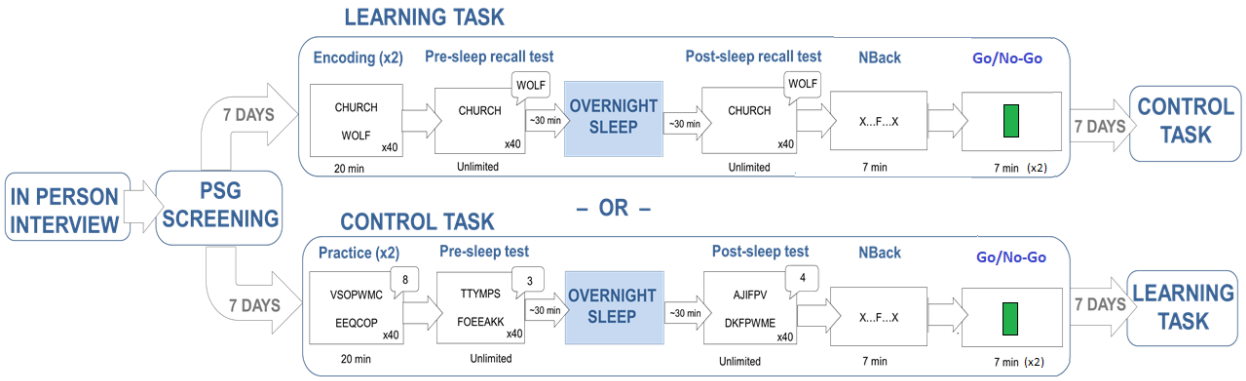

Figure 1. Schematic of the study design. Participants deemed eligible after the in-person interview underwent a first night of PSG screening. If no major sleep disorder was detected, participants returned at least 7 days later for a second recording visit, and then returned at least 7 days after that for a third recording visit. Participants completed daily sleep diary entries and were monitored by wrist actigraphy in the intervening weeks. The second and third recording visits were experimental nights, with a pre-sleep learning (word-pair associates) task night or a non-learning (letter-shape discrimination) control task, with tests counterbalanced across participants to control for order effects. In the learning task, participants were presented with a list of 40 word-pairs, with each list presented twice during encoding. This was followed by a pre-sleep (short-delay) cued recall test, where verbal responses were recorded by a research assistant. In the control task, which was structured identically to the learning task, participants were shown a list of 40 nonsense-word-pairs, with instructions to count the number of curved letters they see on screen (e.g., C, D, and S, but not X, Y, and A). The next morning after overnight sleep, participants completed a post-sleep test of the task they completed the night before. Word-pair pre-sleep and post-sleep tests involved the same pairs of words in a shuffled order; the control task pre- and post-sleep tests each included a unique set of nonsense-word-pairs. After finishing the post-sleep version of whichever task they completed the night before, on both experimental visits the participants completed two additional tasks: N-back (1-back and 2-back) and a Go/No-Go task (data not reported here). After completing all 3 morning tasks the participants were disconnected from the recording equipment.

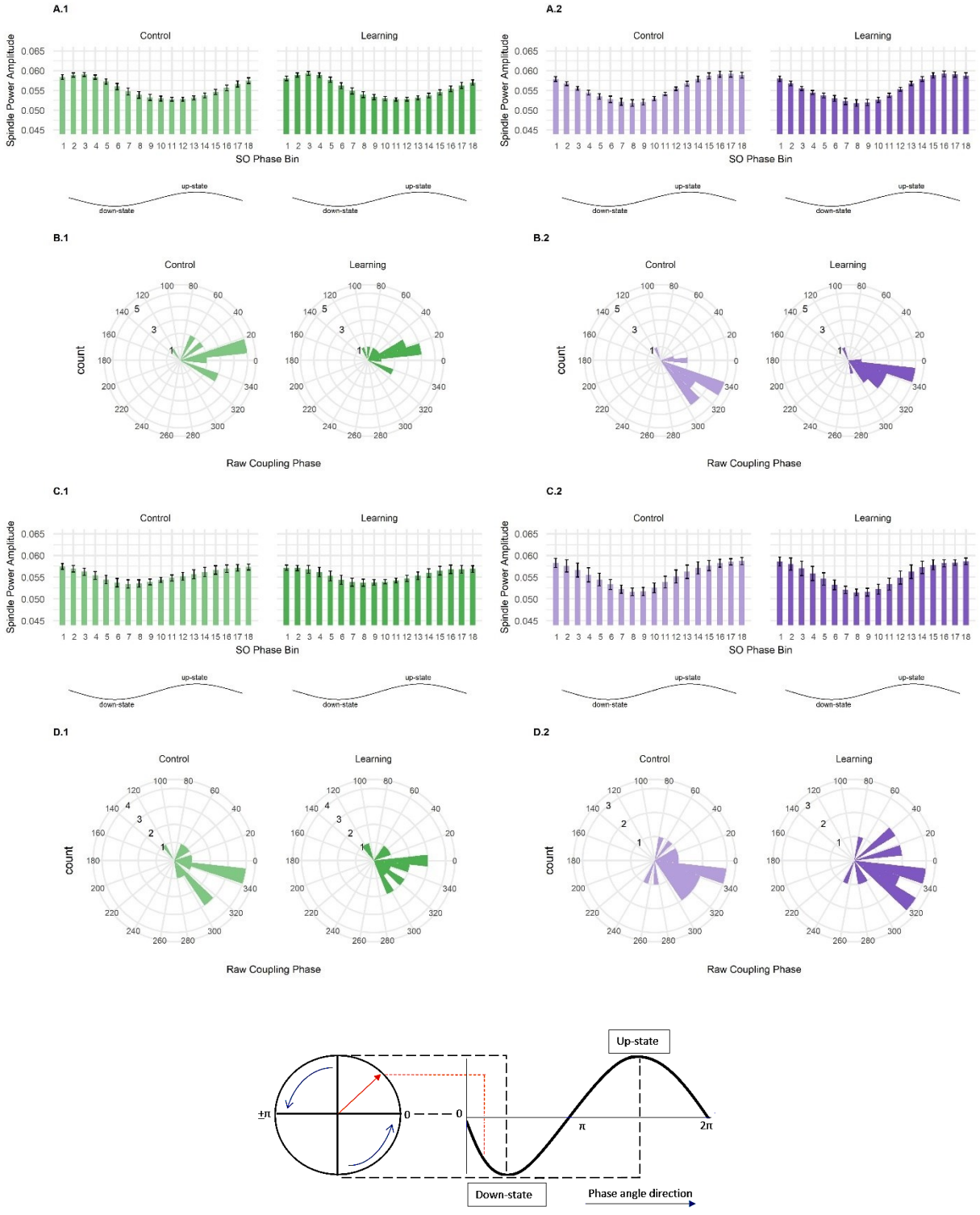

Figure 2. Schematic representation of coupling dynamics on Fz. The Young Adult (YA) group is coloured in green and the Older Adult (OA) group is coloured in purple. The control task night is shown in the faded colour, and the learning task night is shown in the darker colour. The top half of the figure

presents data from Fz on all detected SO events using a fixed bandwidth (9–13 Hz), and the bottom half of the figure presents data using adapted bands (4 Hz bandwidth). **A** and **C**, Phase-amplitude histograms for the control task and learning task night in YAs (A.1 and C.1) and in OAs (A.2 and C.2). Each vertical bar reflects the sigma power mean amplitude (μV; y-axis) across each of the 18 x 20-degree phase bins (x-axis). Error bars are for the standard error of the mean. The corresponding SO oscillation phase is plotted below for reference; the hyperpolarizing SO down-state is pointing down, and is followed by the depolarizing up-state, pointing up. **B** and **D**, Preferred (raw) coupling phase polar plots for the control task and learning task night in YAs (B.1 and D.1) and in OAs (B.2 and D.2). Each coloured bar represents the number of participants with the same overall coupling phase. The count scale (pointing to 130 deg on the circle) is reflected by the concentric rings extending from the center of each circular figure. The depolarizing SO up-state corresponds to 270 deg on the circle (6:00 position) and hyperpolarizing down-state corresponds to 90 deg on the circle (12:00 position), with the phase-angle direction moving counter-clockwise. At the bottom of the figure is a graphical legend of SO phase angle and its relationship with the polar plots, with an example phase in orange (adapted from Ong et al., 2016). Across all the figures, the general pattern shows a sigma power amplitude peaking after the upstate, in the up-to-downstate transition, with power in YAs peaking closer to the downstate and power in OAs peaking closer to the upstate. Analyses with adapted bands suggest that mean amplitude increases across the SO are smaller in YAs, and the raw coupling phases in both groups is more varied/less consistent across subjects relative to analyses with fixed bands.

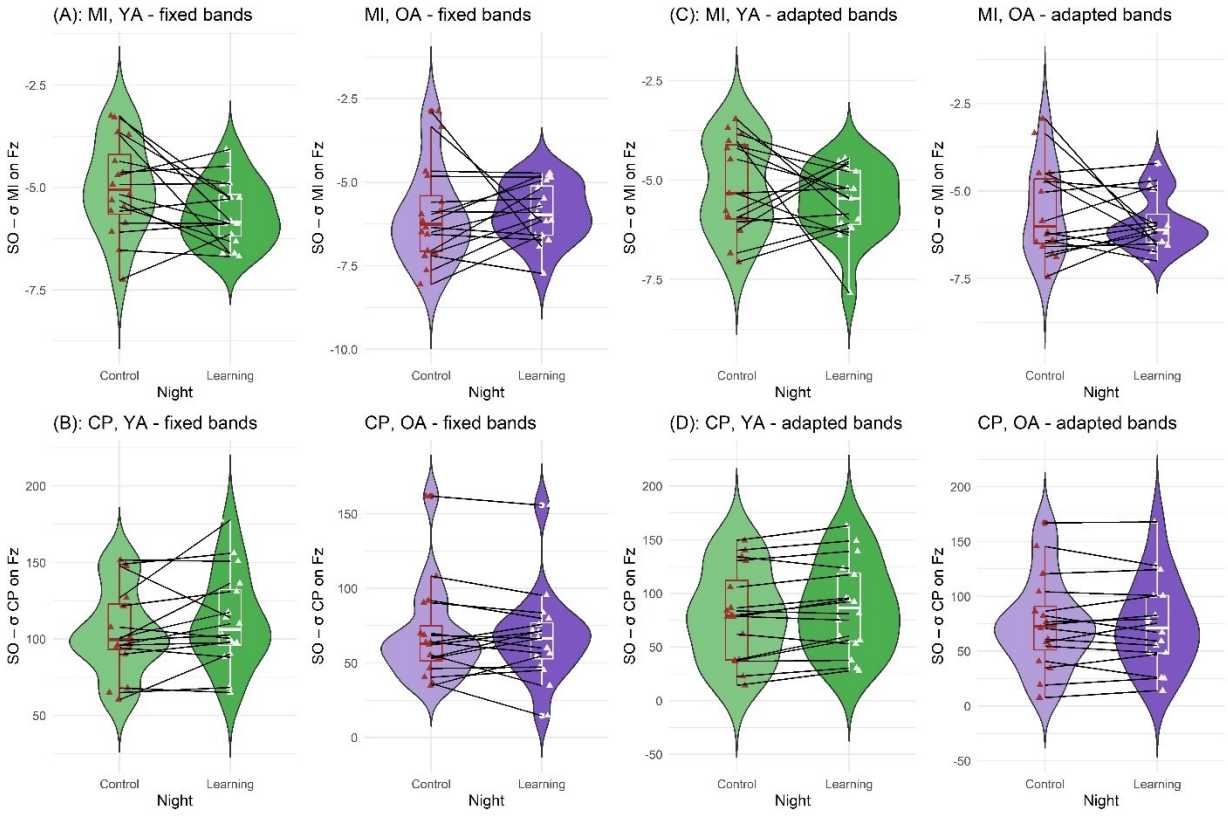

Figure 3. Distributions of MI and CP on Fz. Violin plots showing dispersion of MI (**A** and **C**, top row) and CP (**B** and **D**, bottom row) from Fz and in both bandwidth conditions. The YA group is coloured in green, and the OA group is coloured purple. The control task night is shown in the faded colour, and the learning task night is shown in the darker colour. Fixed bands (9–13 Hz) are presented in the left half of the figure and adapted bands are presented on the right half (4 Hz bandwidth). Inside each violin plot is a boxplot displaying the spread of values in each condition, and the black lines connecting the plots in each panel reflect the night-to-night change in values for each participant. The MI figures suggest that individual values were more varied across nights relative to the CP figures, which show greater night-to-night consistency across participants. There were no significant differences between nights or groups, and no group-by-night interactions for any measure.

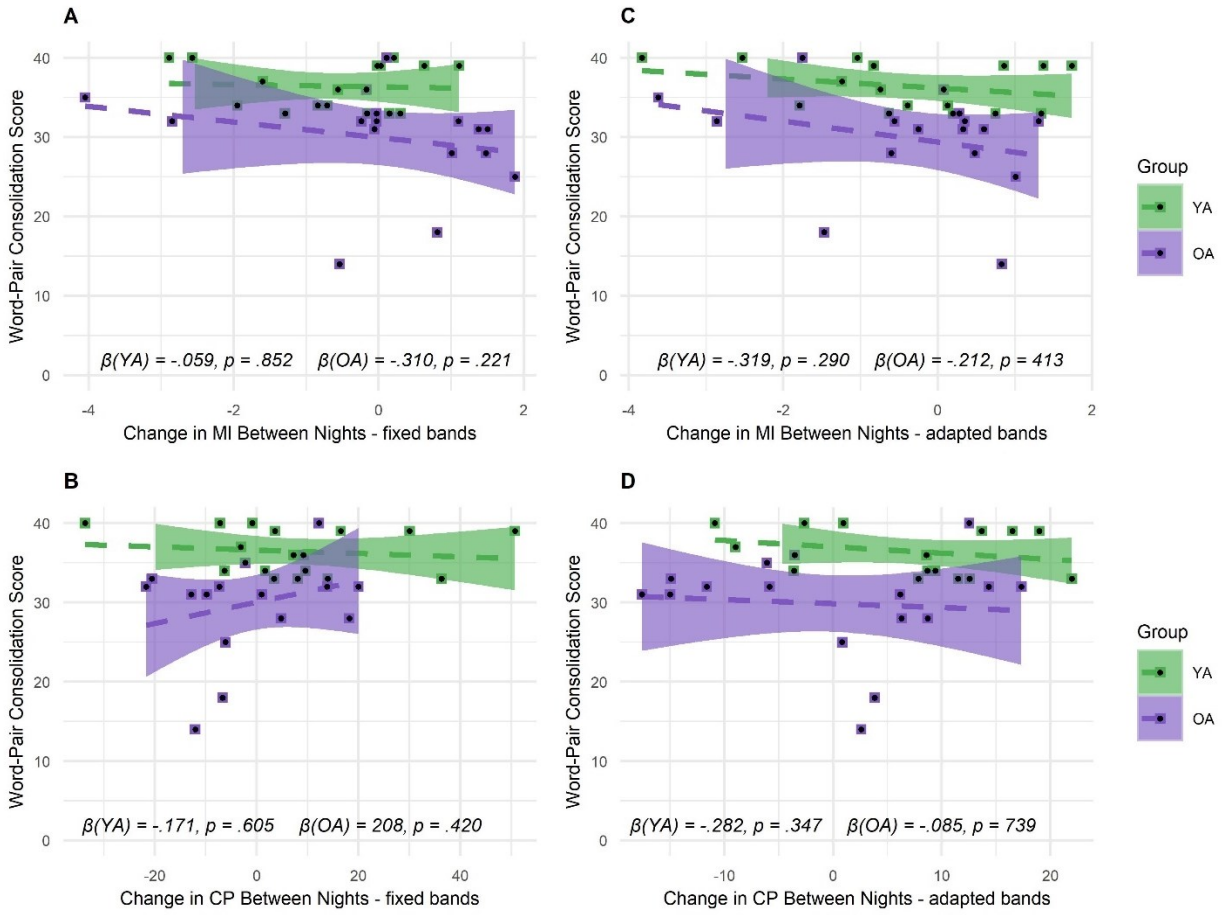

Figure 4. Associations between SO – σ CFC and word-pair Overnight Consolidation scores. Scatterplots displaying association of word-pair memory consolidation score (on y-axis of each plot) with relative change between nights in MI (**A** and **C**) between nights, and relative change in CP (**B** and **D**) from Fz. The YA group is coloured in green, and the OA group is coloured in purple. Coloured ribbons reflect the standard error. Figures **A** and **B** display data with fixed bands for everyone, and Figures **C** and **D** display data with adapted bands. Values of change in MI between nights (rel_MI) above zero reflect greater coupling strength on the learning night, and values of change in CP between nights (rel_CP) below zero reflect a shift in coupling phase *towards* the up-state on the learning night. Standardized coefficient and *p*-value on each plot is from hierarchical regression models examining rel_MI or rel_CP in predicting word-pair scores, controlling for age and sleep apnea severity. There were no significant associations between any coupling measure and our memory consolidation score in either YA or OA group.

Table 1

Demographics and Screening. n(YA) = 16; n(OA) = 16.

	YA		OA		YA vs. OA	
	***M* (SD)**	**Range**	***M* (SD)**	**Range**	***t* (df=30)**	***p***
Demographics						
Age	24.50 (3.31)	19-29	67.44 (6.81)	56-77	-22.68”	.000
Sex (% Female)	56.3%	-	68.8%	-	0.53*	.465
Language (% French)[#]	25.0%	-	25.0%	-	N/A	N/A
Handedness (% Right)	75.0%	-	100%	-	4.57*	.033
Education (years)	17.19 (2.88)	13-24	16.47 (3.91)	9-25	0.59	.558
BMI (kg/m^2)	23.58 (2.81)	18.10-28.60	25.20 (4.38)	19.90-34.60	-1.249”	.223
Assessments/Questionnaires						
MMSE[+]	29.13 (1.13)	27-30	28.81 (1.28)	26-30	0.74	.465
MoCA	28.38 (1.13)	25-30	27.19 (2.11)	22-30	1.88	.070
ISI	1.75 (1.88)	0-7	4.13 (3.44)	0-12	-2.42”	.024
PSQI	2.50 (1.16)	0-4	3.06 (1.18)	0-5	-1.36	.183
ESS	4.81 (2.74)	1-9	4.94 (4.22)	0-14	-0.10	.921
Stop-BANG	0.56 (0.51)	0-2	1.56 (0.63)	1-3	-4.93	.000
MEQ	55.25 (9.31)	40-69	64.25 (9.49)	40-80	-2.71	.011
Depression	2.38 (2.36)	0-7	4.38 (3.91)	0-12	-1.75”	.090
Anxiety	2.00 (2.63)	0-8	1.94 (2.98)	0-10	0.06	.950

Note: MMSE, Mini Mental State Exam; *MoCA*, Montreal Cognitive Assessment; *ISI*, Insomnia Severity Index; *PSQI*, Pittsburgh Sleep Quality Index; *ESS* Epworth Sleepiness Scale ; MEQ, Morningness-Eveningness Questionnaire; *Depression (*YA*)* Beck Depression Inventory and (OA) Geriatric Depression Scale; *Anxiety,* (YA) Beck Anxiety Inventory and (OA) Geriatric Anxiety Inventory; Note that depression and anxiety scales were each unique to both groups, however each questionnaire is based on a total overall score, where higher scores reflect a greater number or severity of symptoms. *M,* mean; *SD,* standard deviation. [*], Chi-Square statistic; [#], Analysis for Language could not be performed due to a cell count <5. [+], n(YA) = 15. “, non-equal variances.

Table 2

Sleep architecture of EEG recording nights (control night, EEGc; learning/memory task night, EEGm) and between-group comparisons. n(YA) = 16; n(OA) = 16.

	YA		OA		YA vs. OA		EEGc vs. EEGm	
	EEGc (*M*(SD))	EEGm (*M*(SD))	EEGc (*M*(SD))	EEGm (*M*(SD))	*F* (1, 28)	*p*	*F* (1, 28)	*p*
TST (mins)	399.34 (53.76)	410.84 (32.49)	393.66 (44.58)	402.03 (37.28)	0.328	.571	1.423	.243
SE (%)	92.12 (5.21)	93.77 (3.48)	86.82$^{+\,*}$ (6.39)	88.39$^{+\,**}$ (6.19)	11.955	.002	2.373	.135
SOL (mins)	11.51 (9.03)	12.08 (8.06)	9.33 (7.47)	10.35 (8.72)	0.526	.474	0.324	.574
% N1	7.20 (4.26)	7.26 (4.05)	11.28* (6.94)	11.49* (5.18)	6.921	.014	0.061	.807
% N2	50.83 (7.82)	51.23 (7.59)	58.60** (6.57)	59.47** (6.41)	11.901	.002	0.350	.559
% N3	22.02 (7.40)	21.86 (8.44)	12.50** (8.23)	11.58*** (5.56)	15.034	.001	0.642	.430
% REM	19.95 (4.13)	19.65 (5.01)	17.62 (4.90)	17.47 (4.50)	2.819	.104	0.066	.799
WASO (mins)	16.91 (13.29)	14.94 (12.66)	41.47$^{+\,**}$ (29.31)	39.69$^{+\,**}$ (26.73)	14.826	.001	0.265	.610
SFI (#/hr)	7.20 (2.48)	7.55 (2.53)	11.12$^{+\,**}$ (3.41)	11.21** (2.87)	16.257	<.001	0.498	.486

Note: YA, Young Adults; OA, Older Adults; *M*, mean; SD, standard deviation. TST, total sleep time; SE, sleep efficiency; SOL, sleep onset latency; % N1, percent of non-rapid-eye-movement (NREM) stage 1; % N2, percent of NREM 2; % N3, percent of NREM 3; % REM, percent of rapid-eye-movement sleep; WASO, wake after sleep onset; SFI, sleep fragmentation index; mins, minutes; hr, hour. *F*-statistic and *p*-values are for main effects of Group (YA vs. OA) and Night (EEGc vs. EEGm, repeated measure) in a 2x2 ANCOVA, controlling for age and sleep apnea severity. There were no significant Group X Night interactions. $^{+}$ denotes a significant Levene's test for equality of (error) variances on a given night. * denotes a significant difference between groups on a given night, based on independent-samples t-tests. There were no significant differences across nights within either group, based on paired-samples t-tests.

Table 3

Event-detected NREM Slow Oscillations (0.5–1.25 Hz) on Fz between groups and across study nights. *n*(YA) = 15; *n*(OA) = 12.

	YA		**OA**		**YA vs. OA**		**EEGc vs. EEGm**	
	EEGc (*M*(SD))	**EEGm (*M*(SD))**	**EEGc (*M*(SD))**	**EEGm (*M*(SD))**	***F* (1, 28)**	***p***	***F* (1, 28)**	***p***
Count	1935.44 (437.51)	2030.12 (464.07)	1947.31 (438.45)	1981.75 (428.83)	0.019	.892	1.270	.269
Density (/30s)	3.33 (0.62)	3.37 (0.64)	3.48 (0.66)	3.45 (0.51)	0.310	.582	0.001	.970
Duration (s)	1.36 (0.06)	1.36 (0.05)	1.38 (0.06)	1.38 (0.07)	0.517	.478	0.027	.870
Peak-to-Peak (μV)	216.05 (52.73)	208.99 (47.10)	134.61 (35.41)	130.51 (32.14)	34.327	<.001	8.401	.007
Energy ($\mu V^2 s$)	1936.19 (1233.84)	1748.11 (997.80)	640.98$^+$ (394.74)	600.40$^+$ (355.65)	18.204	<.001	7.350	.011
Peak Energy Freq (Hz)	0.75 (0.05)	0.74 (0.05)	0.73 (0.07)	0.73 (0.07)	0.632	.433	0.117	.735

Note. YA, Young Adults; OA, Older Adults; *M*, mean; SD, standard deviation. Freq, frequency. s, seconds; μV; microvolts; Hz, Hertz. *F*-statistic and *p*-values are for main effects of Group (YA vs. OA) and Night (EEGc vs. EEGm, repeated measure) in a 2x2 ANCOVA, controlling for age and sleep apnea severity. Covariates were mean-centered for each group separately. There were no Group X Night interactions. A $^+$ denotes a significant Levene's test for equality of (error) variances across groups on a given night.

Table 4

Event-detected NREM sleep spindles on Fz using fixed bands (9–13 Hz) and adapted bands between groups and across study nights. n(YA) = 16; n(OA) = 16.

	YA		OA		YA vs. OA		EEGc vs. EEGm	
	EEGc (*M*(SD))	**EEGm (*M*(SD))**	**EEGc (*M*(SD))**	**EEGm (*M*(SD))**	***F* (1, 28)**	***p***	***F* (1, 28)**	***p***
Fixed bands								
Count	757.81 (132.56)	806.76 (176.72)	680.19 (170.00)	709.31 (160.74)	3.160	.086	4.627	.040
Density (/30s)	1.311 (0.20)	1.34 (0.21)	1.21 (0.22)	1.24 (0.23)	1.908	.178	3.928	.057
Duration (s)	0.80 (0.04)	0.80 (0.03)	0.76 (0.05)	0.76 (0.05)	5.422	.027	0.022	.883
Peak-to-Peak (μV)	149.71 (34.51)	150.48 (35.38)	100.59 (23.41)	95.97 (21.17)	29.456	<.001	1.348	.255
Energy ($\mu V^2 s$)	215.20 (61.33)	217.33 (55.70)	153.72 (87.39)	148.81 (82.77)	8.217	.008	0.737	.398
Peak Energy Freq (Hz)	10.92 (0.54)	10.91 (0.58)	10.47 (0.64)	10.47 (0.62)	4.347	.046	0.019	.891
Adapted bands								
Count	784.94 (153.12)	835.19 (188.32)	636.56 (177.66)	659.65 (167.39)	9.816	.004	3.662	.066
Density (/30s)	1.36 (0.23)	1.39 (0.23)	1.14 (0.26)	1.15 (0.26)	8.195	.008	2.869	.101
Duration (s)	0.80 (0.04)	0.80 (0.04)	0.75 (0.05)	0.75 (0.05)	9.684	.004	0.013	.909
Peak-to-Peak (μV)	143.62 (34.38)	143.54 (35.05)	100.55 (23.91)	96.63 (21.34)	21.515	<.001	1.371	.251
Energy ($\mu V^2 s$)	199.41 (57.46)	200.30 (56.26)	149.18 (86.77)	145.08 (84.94)	5.029	.033	0.176	.678
Peak Energy Freq (Hz)	11.18 (0.78)	11.16 (0.81)	10.53 (0.81)	10.53 (0.79)	5.467	.027	0.038	.846

Note. YA, Young Adults; OA, Older Adults; *M*, mean; SD, standard deviation. Spindles detected using a fixed band (9–13 Hz) or using individually adapted bandwidths based on preliminary analysis of spectral

peaks (bandwidth = 4 Hz; See Figure S1). Freq, frequency. s, seconds; μV; microvolts; Hz, Hertz. *F*-statistic and *p*-values are for main effects of Group (YA vs. OA) and Night (EEGc vs. EEGm, repeated measure) in a 2x2 ANCOVA, controlling for age and sleep apnea severity. Covariates were mean-centered for each group separately. There were no significant Group X Night interactions.

Table 5

MI and CP on Fz from NREM between study nights. n(YA) = 16; *n*(OA) = 16.

	MI		**CP**	
	EEGc (*M*(*SD*))	**EEGm (*M*(*SD*))**	**EEGc (*M*(*SD*))**	**EEGm (*M*(*SD*))**
			YA	
SO – σ (*f*)	-4.99 (1.16)	-5.63 (0.78)	104.64 (28.53)	112.77 (31.11)
SO – σ (*a*)	-5.15 (1.17)	-5.57 (0.91)	79.89 (43.22)	87.27 (42.30)
			OA	
SO – σ (*f*)	-5.99 (1.45)	-5.91 (0.88)	68.78 (32.19)	67.53 (30.80)
SO – σ (*a*)	-5.54 (1.32)	-5.90 (0.80)	75.27 (43.13)	75.13 (41.67)

Note. YA, Young Adults; OA, Older Adults; *M*, mean; *SD*, standard deviation. MI, log-transformed modulation index. SO, slow oscillation (0.5–1.25 Hz); σ *(f),* fixed sigma band (9–13 Hz); σ *(a)*, adapted sigma band (bandwidth = 4 Hz). Pearson's correlations, examining the across-night stability of MI and CP from both fixed- and adapted-band conditions, revealed that MI was not correlated between nights in either group or condition (YA group: [MI (*f*): $r = 0.346$, $p = 0.190$; MI (*a*): $r = -0.030$, $p = 0.912$]; OA group: [MI (*f*): $r = 0.148$, $p = 0.584$; MI (*a*): $r = 0.200$, $p = 0.457$]). By contrast, CP was highly stable between nights in both groups and in each band-pair condition (YA group: [CP (*f*): $r = 0.790$, $p < 0.001$; CP (*a*): $r = 0.974$, $p < 0.001$], OA group: [CP (*f*): $r = 0.914$, $p < 0.001$; CP (*a*): $r = 0.967$, $p < 0.001$]).

Table 6

Between-group and across-night comparison of NREM SO-sigma MI and CP (fixed and adapted) on Fz separated by band-pair. n(YA) = 16; *n*(OA) = 16.

	Type III SS	df	Mean Square	*F*	*p*	Partial η^2
			MI			
SO – σ (*f*)						
Night (EEGc vs. EEGm)	1.229	1	1.229	1.198	.283	.041
Group (YA vs. OA)	*6.533*	*1*	*6.533*	*5.148*	*.031*	*.155*
Night X Age	0.000	1	0.000	0.000	.992	.000
Night X AHI	0.001	1	0.001	0.001	.970	.000
Group X Night	2.045	1	2.045	1.993	.169	.066
Error (Night)	28.722	28	1.026			
SO – σ (*a*)						
Night (EEGc vs. EEGm)	2.419	1	2.419	2.241	.146	.074
Group (YA vs. OA)	2.080	1	2.080	1.705	.202	.057
Night X Age	0.282	1	0.282	0.261	.614	.009
Night X AHI	0.877	1	0.877	0.812	.375	.028
Group X Night	0.010	1	0.010	0.009	.924	.000
Error (Night)	30.223	28	1.079			
			CP			
SO – σ (*f*)						
Night (EEGc vs. EEGm)	0.001	1	0.001	0.145	.706	.005
Group (YA vs. OA)	**0.832**	**1**	**0.832**	**16.151**	**<.001**	**.366**
Night X Age	<0.001	1	<0.001	0.004	.952	.000
Night X AHI	0.000	1	0.000	0.073	.789	.003
Group X Night	0.010	1	0.010	1.532	.226	.052
Error (Night)	0.182	28	0.006			
SO – σ (*a*)						
Night (EEGc vs. EEGm)	*0.024*	*1*	*0.024*	*4.409*	*.045*	*.136*
Group (YA vs. OA)	0.060	1	0.060	0.351	.558	.012
Night X Age	0.001	1	0.001	0.246	.624	.009
Night X AHI	0.001	1	0.001	0.263	.612	.009
Group X Night	0.009	1	0.009	1.630	.212	.055
Error (Night)	0.152	28	0.005			

Note. SO, slow oscillation (0.5–1.25 Hz); σ *(f),* fixed sigma band (9–13 Hz); σ (*a*), adapted sigma (bandwidth = 4 Hz). MI, log-transformed modulation index. *F*-statistic and *p*-value are for the main effect of Night from a 2 (Night) x 2 (Group) ANCOVA, with control and learning nights as a repeated measure, controlling for age and sleep apnea severity. Values in **bold** denote results that reached or surpassed Bonferroni-adjusted *p*-value (.006). Values in *italics* denote a trend effect/marginal change at $p < .05$.

Table 7

Prediction of word-pair Overnight Consolidation by relative change between nights in SO-sigma MI and CP on Fz. n(YA) = 16; *n*(OA) = 16.

Band pair	**MI**					**CP**				
	F	**ΔR^2**	***B* (*SE*)**	***β***	***p***	***F***	**ΔR^2**	***B* (*SE*)**	***β***	***p***
YA										
SO – σ (*f*)	0.014	0.003	-0.151 (0.789)	-.059	.852	0.097	0.023	-0.026 (0.049)	-.171	.605
SO – σ (*a*)	0.410	0.092	-0.624 (0.564)	-.319	.290	0.322	0.074	-0.085 (0.087)	-.282	.347
OA										
SO – σ (*f*)	1.977	0.093	-1.261 (0.976)	-.310	.221	1.551	0.042	0.102 (0.122)	.208	.420
SO – σ (*a*)	1.561	0.043	-0.974 (1.149)	-.212	.413	1.297	0.007	-0.050 (0.147)	-.085	.739

Note. YA, Young Adults; SO, slow oscillation (0.5–1.25 Hz); σ (*f*), fixed sigma band (9–13 Hz); σ *(a)*, adapted sigma band (bandwidth = 4 Hz). SO(+) – σ reflects SO events joined with a detected spindle; SO(+) – σ reflects SO events not joined with a detected spindle. MI, log-transformed modulation index. *F*-statistic, ΔR^2, *B (SE), β,* and *p*-value are hierarchical regression models (Model 2) with the MI value of interest as the independent variable predicting word-pair recall performance, controlling for age and sleep apnea severity. Values in **bold** denote results that reached or surpassed Bonferroni-adjusted *p*-value (.006). Values in *italics* denote a trend effect/marginal change at $p < .05$. *B*, unstandardized coefficient. *β*, standardized coefficient; ΔR^2, change in proportion of explained variance; *SE*, standard error.

Table 8

Hierarchical regression to predict word-pair Consolidation Score by SO-sigma MI and CP interaction during the learning night, from Fz. n(YA) = 16; *n*(OA) = 16.

	YA						OA					
Band pair	***F* (df)**	***p***	**ΔR^2**	***B* (*SE*)**	***β***	***p*(*β*)**	***F* (df)**	***p***	**ΔR^2**	***B* (*SE*)**	***β***	***p*(*β*)**
SO – σ (*f*) (base)												
MI [a]	-		-	0.015 (1.238)	.004	.990	-		-	-0.136 (3.324)	-.019	.968
CP [a]	-		-	0.024 (0.033)	.253	.483	-		-	-0.104 (0.075)	-.499	.193
MI x CP	0.138 (5, 15)	.979	0.064	0.002 (0.050)	.016	.962	1.148 (5, 15)	.397	0.127	0.078 (0.100)	.275	.455
SO – σ (*a*) (base)												
MI [a]	-		-	-0.828 (1.121)	-.255	.477	-		-	-1.467 (3.105)	-.182	.647
CP [a]	-		-	-0.009 (0.023)	-.131	.703	-		-	-0.040 (0.053)	-.257	.473
MI x CP	0.200 (5, 15)	.955	0.091	0.013 (0.032)	.144	.679	1.120 (5, 15)	.409	0.121	-0.011 (0.057)	-.070	.857

Note. SO (0.5–1.25 Hz); σ (*f*), fixed sigma band (9–13 Hz); σ *(a)*, adapted sigma band (bandwidth = 4 Hz). MI, Modulation Index; CP, absolute coupling phase distance from the SO up-state. *F*-statistic, *p*-value, ΔR^2, *B (SE), β,* and *p*(*β*) are from hierarchical regression models to predict word-pair consolidation (Model 2) with centered MI and CP values alongside their interaction. Age and apnea-hypopnea index (measured on first (PSG) night) were entered in Model 1. *F*-statistic and ΔR^2 is presented only for the final model with interaction term. ΔR^2, change in proportion of explained variance; SE, standard error. *B*, unstandardized coefficient. *β*, standardized coefficient. *p*(*β*) is *p*-value associated with the standardized regression coefficient for the independent variable, controlling for other model predictors. Values in **bold** denote results that surpassed the conventional critical *p*-value (< .05). "(base)" refers to the baseline interaction model, containing two mean-centered predictors and their product as an interaction term; models in the two subsequent rows present follow-up analyses to examine moderating effects of MI when a significant interaction was found in the base model. [a], mean-centered main-effect predictor.

SUPPLEMENTAL MATERIAL – STUDY 2

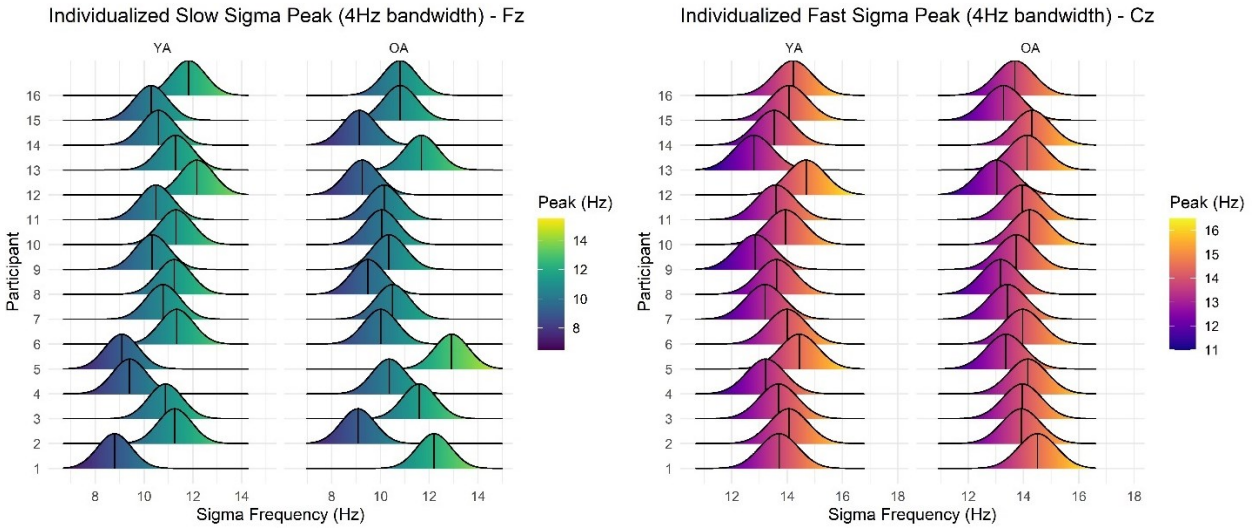

Figure S1. Ridgeline plots displaying the individualized (adapted) sigma peaks from each participant on channel Fz (slow sigma frequency, on left) and channel Cz (fast sigma frequency, on right). Peaks on Fz were similarly varied across participants in the Young Adult (YA) and Older Adult (OA) groups, whereas peaks on Cz were more consistent across subjects within and between groups. The peaks were significantly different between groups on channel Fz (*M*(YA) = 11.48 Hz; *M*(OA) = 10.72 Hz; *t*(30) = 2.333, *p* = .027) but not on Cz (*M*(YA) = 13.73 Hz; *M*(OA) = 13.80 Hz; *t*(30) = -0.431, *p* = .669).

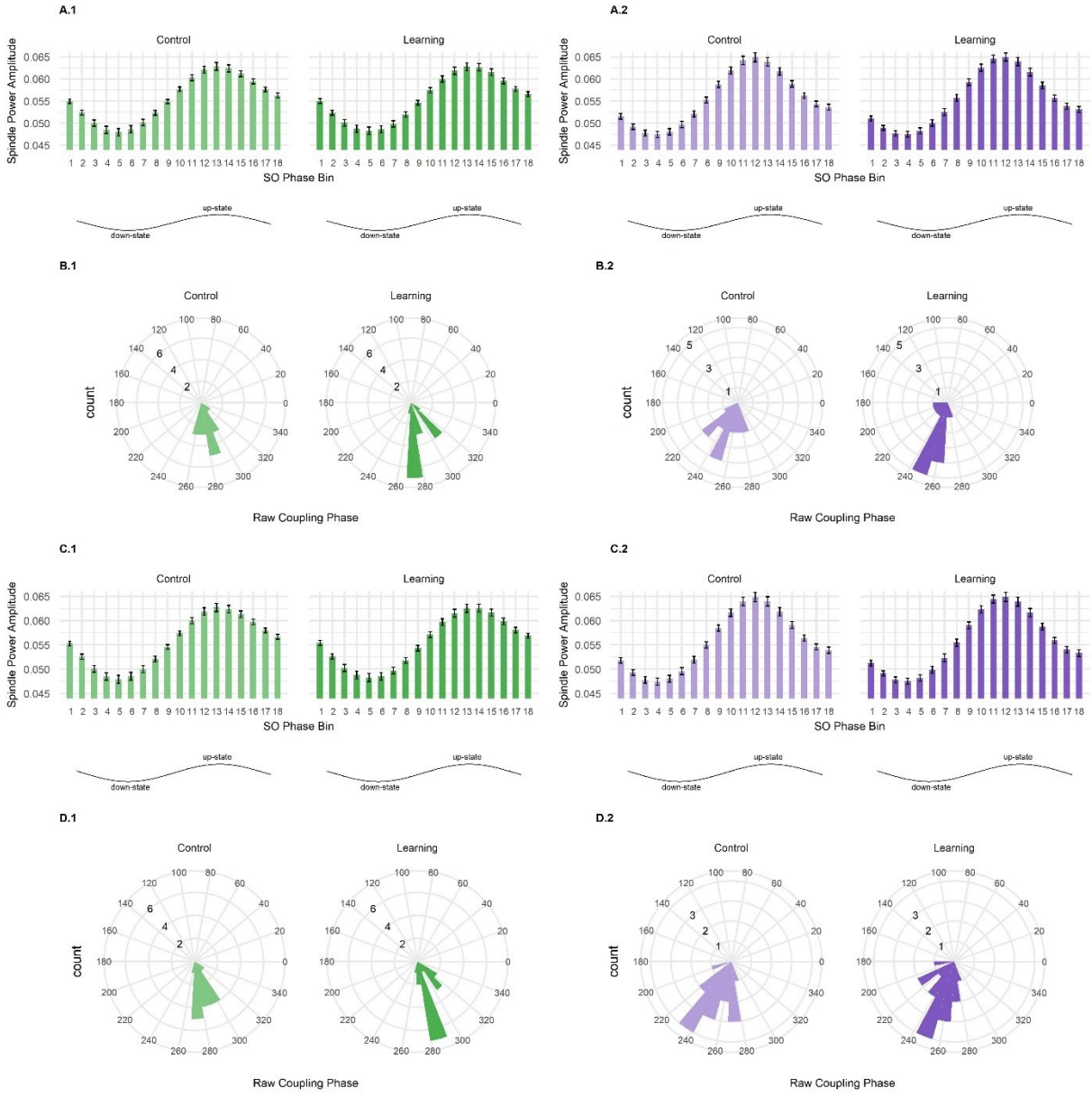

Figure S2. Schematic representation of coupling dynamics on Cz. The YA group is coloured in green and the OA group is coloured in purple. The control task night is shown in the faded colour, and the learning task night is shown in the darker colour. The top half of the figure presents data from Cz using a fixed bandwidth (12–16 Hz), and the bottom half of the figure presents data using adapted bands (4 Hz bandwidth). **A** and **C**, Phase-amplitude histograms for the control task and learning task night in YAs (A.1 and C.1) and in OAs (A.2 and C.2). Each vertical bar reflects the sigma power mean amplitude (μV; y-axis) across each of the 18 x 20-degree phase bins (x-axis). Error bars are for the standard error of the

mean. The corresponding SO oscillation phase is plotted below for reference. **B** and **D**, Preferred (raw) coupling phase polar plots for the control task and learning task night in YAs (B.1 and D.1) and in OAs (B.2 and D.2). Each coloured bar represents the number of participants with the same overall coupling phase. The count scale (pointing to 130 deg on the circle) is reflected by the concentric rings extending from the center of each circular figure. Refer to Figure 2 for a description and legend for interpreting the circular (polar) plots. Across all the figures, spindle activity coupled as expected across both groups, with rises in sigma power mostly during or after the up-state in YAs and earlier in the rising SO phase (before the up-state) in OAs. Unlike Figure 2 with data from Fz, there were fewer differences in the coupling patterns between fixed- and adapted-band conditions.

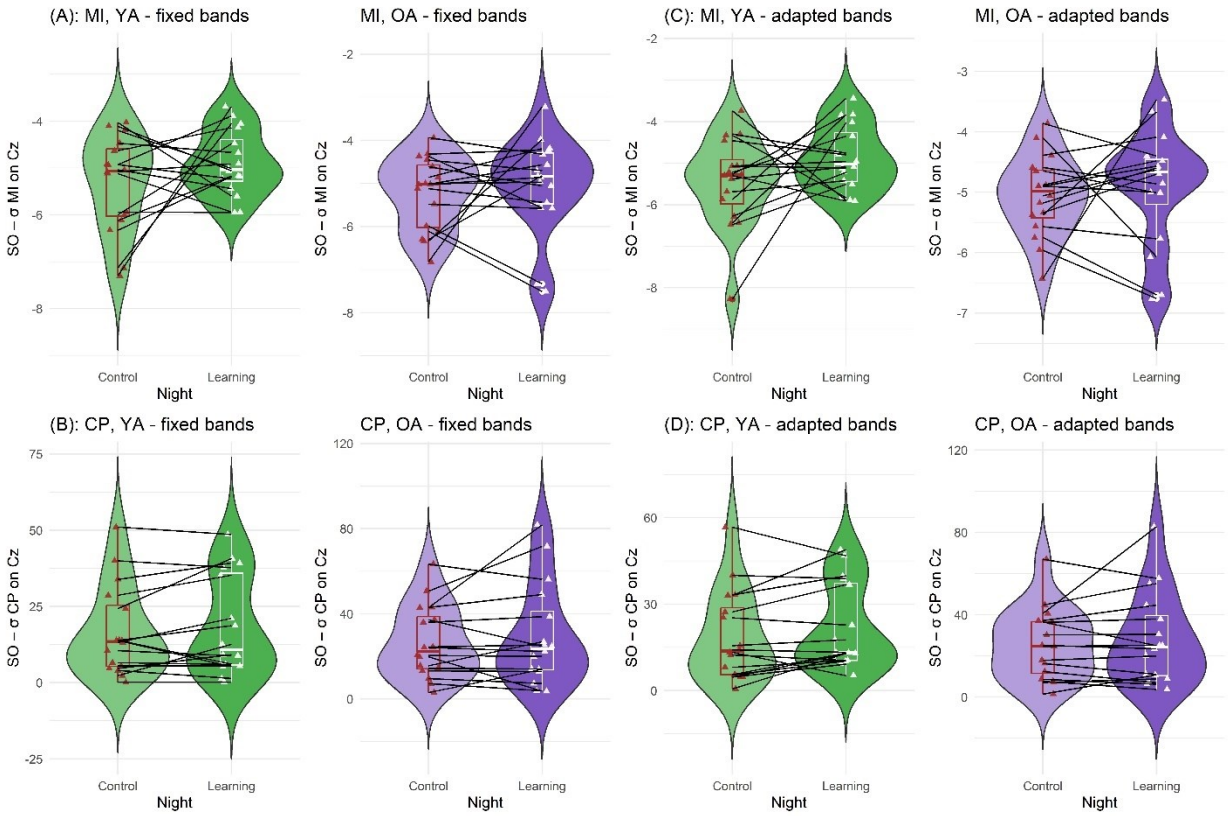

Figure S3. Distributions of MI and CP on Cz. Violin plots displaying dispersion of MI (**A** and **C**, top row) and CP (**B** and **D**, bottom row) from Cz and in both bandwidth conditions. The YA group is coloured in green and the OA group is coloured in purple. The control task night is shown in the faded colour, and the learning task night is shown in the darker colour. The left half of the figure presents data from Fz using a fixed bandwidth (12–16 Hz), and the right half presents data using adapted bands (4 Hz bandwidth). Inside each violin plot is a boxplot displaying the spread of values in each condition, and the black lines connecting the plots in each panel reflect the night-to-night change in values for each participant. Consistent with Figure 3, MI measures were more varied across nights relative to CP in both groups. There were no significant differences between nights or groups, and no group-by-night interactions for any measure.

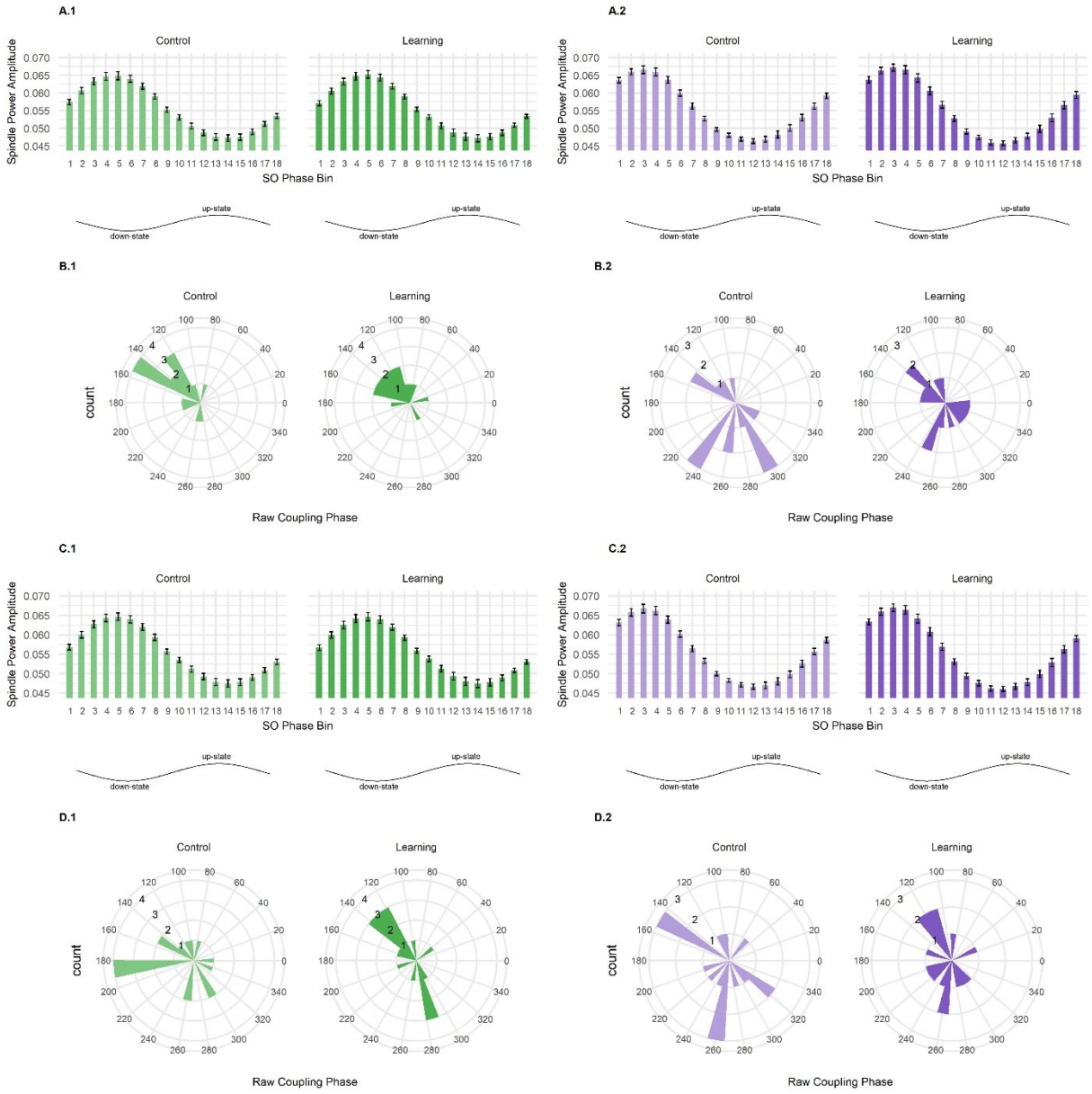

Figure S4. Schematic representation of coupling dynamics on Fz from SO events that were joined with a detected sleep spindle (SO+ events). The YA group is coloured in green and the OA group is coloured in purple. Figure is arranged with the same conventions as in Figure 2 and Figure S2. The top half of the figure presents data using a fixed bandwidth (9–13 Hz), and the bottom half of the figure presents data using adapted bands (4 Hz bandwidth). **A** and **C**, Phase-amplitude histograms for the control task and learning task night in YAs (A.1 and C.1) and in OAs (A.2 and C.2). **B** and **D**, Preferred (raw) coupling

phase polar plots for the control task and learning task night in YAs (B.1 and D.1) and in OAs (B.2 and D.2). Refer to Figure 2 for a description and legend for interpreting the circular (polar) plots. Compared to Figure 2, with data from Fz on all detected SO events, rises in sigma amplitude across the SO(+) events was more clearly clustered towards the SO down-state peak. Unlike Figure 2, showing that slow spindle activity clustered after the up-state, preferred coupling phase on SO(+) events in each sample was more widely distributed across the SO phase, showing a generally uniform circular distribution in all cases except for SO – σ (*f*) in YAs (confirmed using Rayleigh tests of non-uniform distributions; see Table S19).

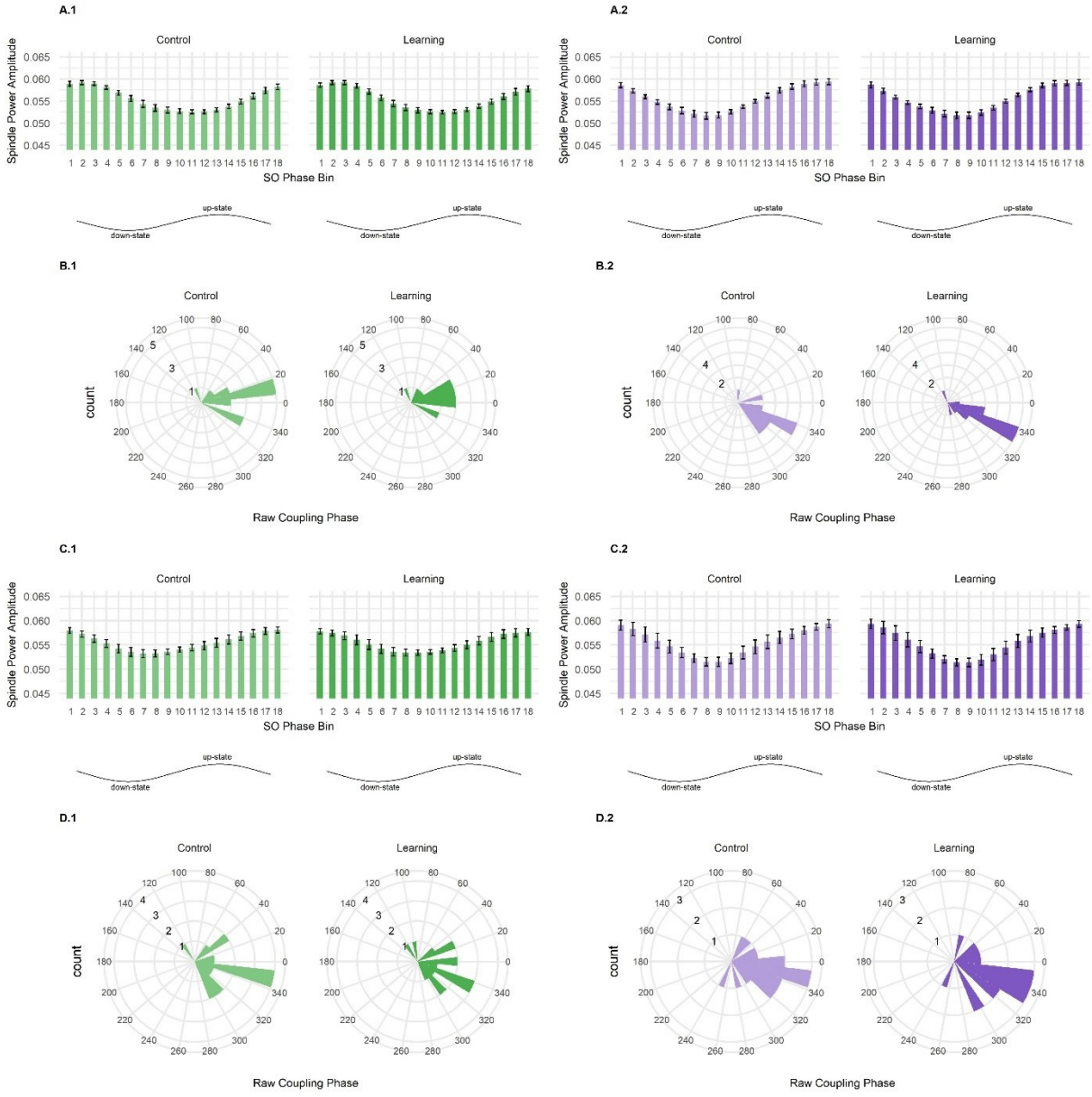

Figure S5. Schematic representation of coupling dynamics on Fz from isolated SO events that were not joined with a detected sleep spindle (SO- events). The YA group is coloured in green and the OA group is coloured in purple. Figure is arranged with the same conventions as in Figure 2 and Figure S2. The top half of the figure presents data using a fixed bandwidth (9–13 Hz), and the bottom half of the figure presents data using adapted bands (4 Hz bandwidth). **A** and **C**, Phase-amplitude histograms for the control task and learning task night in YAs (A.1 and C.1) and in OAs (A.2 and C.2). **B** and **D**, Preferred (raw) coupling phase polar plots for the control task and learning task night in YAs (B.1 and D.1) and in OAs

(B.2 and D.2). Refer to Figure 2 for a description and legend for interpreting the circular (polar) plots. Consistent with Figure 2, showing data from Fz on all detected SO events, sigma power amplitude on SO(-) events tended to peak more evenly across the SO phase-bins, and with a peak that fell generally after the up-state. Preferred coupling phase with slow spindle activity also showed the same pattern as in Figure 2 with all SO events, both in the coupling pattern across the two groups, and in differences within each group between the fixed- and adapted-band conditions (i.e., more consistent vs. more varied coupling phase, respectively).

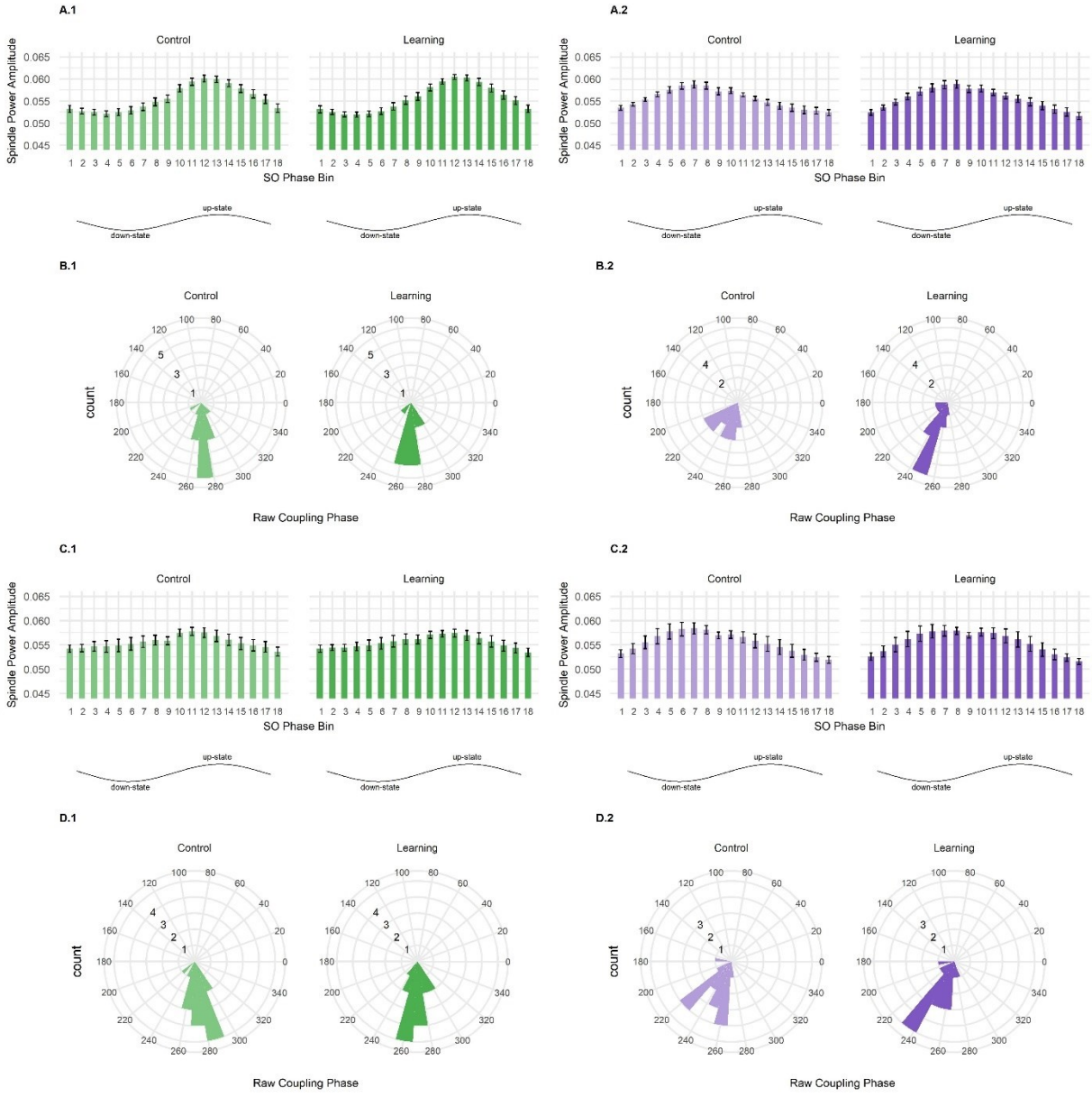

Figure S6. Schematic representation of coupling dynamics on Cz from SO events that were joined with a detected sleep spindle (SO+ events). The YA group is coloured in green and the OA group is coloured in purple. Figure layout and each included plot holds the same conventions as in Figure 2 and Figure S2. The top half of the figure presents data using a fixed bandwidth (12–16 Hz), and the bottom half of the figure presents data using adapted bands (4 Hz bandwidth). **A** and **C**, Phase-amplitude histograms for the control task and learning task night in YAs (A.1 and C.1) and in OAs (A.2 and C.2). **B** and **D**, Preferred (raw) coupling phase polar plots for the control task and learning task night in YAs (B.1 and D.1) and in

OAs (B.2 and D.2). Refer to Figure 2 for a description and legend for interpreting the circular (polar) plots. Consistent with Figure S2, showing data from Cz on all detected SO events, rises in sigma power amplitude across the SO(+) phase-bins generally peaked during or after the up-state in YAs, and earlier in the rising SO phase in OAs (in this case, peaking even earlier in the down-to-up-state transition compared to measures from all SO events). However, unlike Figure S2, and especially in the adapted-band condition for YAs, rises in sigma power amplitude appeared wider/more spread out across the SO(+) phase-bins, and with less clearly defined peaks. However, preferred coupling phase with fast spindle activity was consistent with Figure S2, in both fixed- and adapted-band conditions.

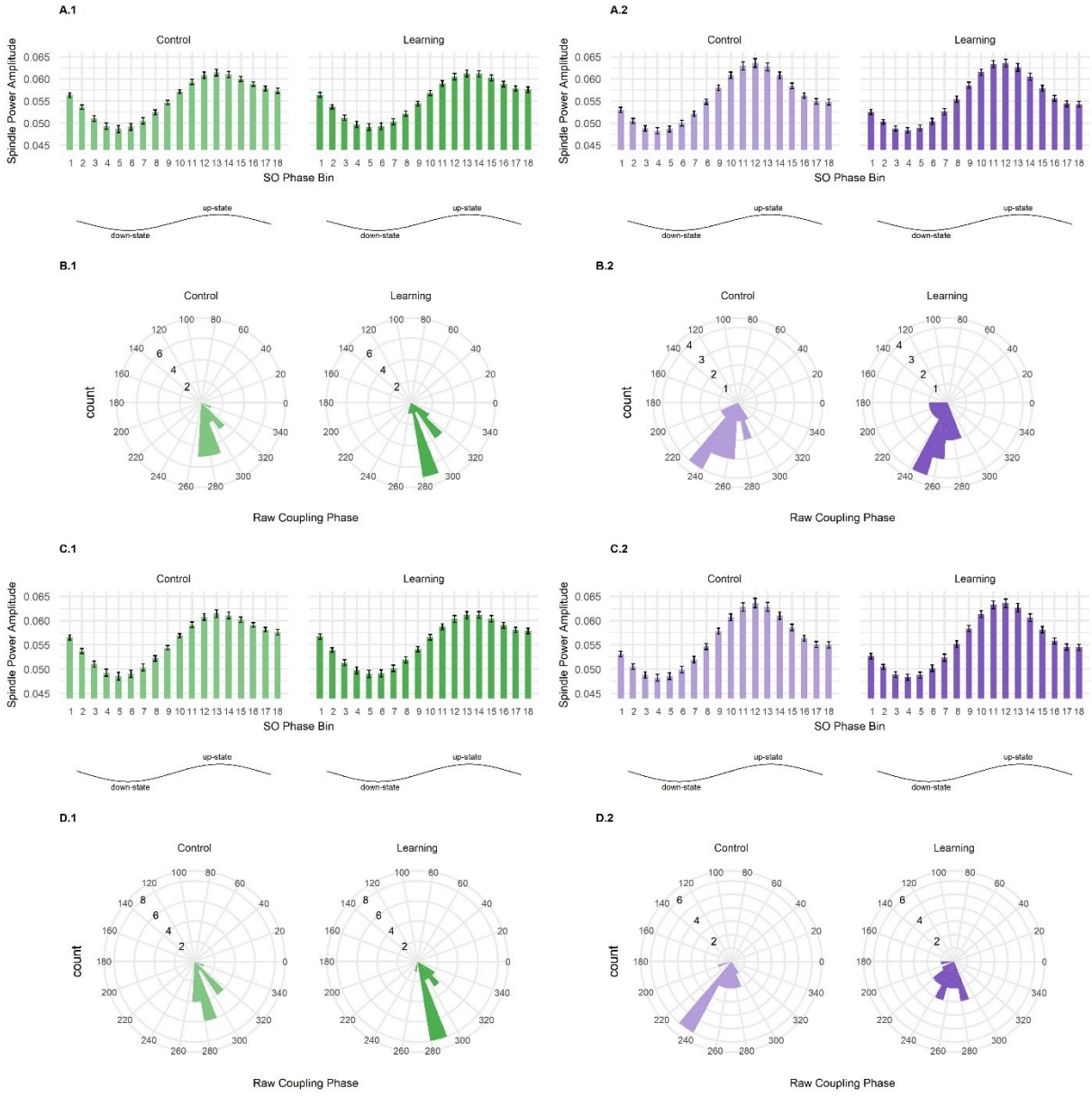

Figure S7. Schematic representation of coupling dynamics on Cz from isolated SO events that were not joined with a detected sleep spindle (SO- events). The Young Adult (YA) group is coloured in green and the Older Adult (OA) group is coloured in purple. The control task night is shown in the faded colour, and the learning task night is shown in the darker colour. The top half of the figure presents data using a fixed bandwidth (12–16 Hz), and the bottom half of the figure presents data using adapted bands (4 Hz bandwidth). **A** and **C**, Phase-amplitude histograms for the control task and learning task night in YAs (A.1 and C.1) and in OAs (A.2 and C.2). Same conventions as in Figure 2 and Figure S2. **B** and **D**,

Preferred (raw) coupling phase polar plots for the control task and learning task night in YAs (B.1 and D.1) and in OAs (B.2 and D.2). Same conventions as in Figure 2 and Figure S2. Refer to Figure 2 for a description and legend for interpreting the circular (polar) plots. Consistent with Figure S2, showing data from Cz on all detected SO events, rises in sigma power amplitude across the SO(-) events occurred during or after the up-state in YAs and earlier in the rising SO phase (before the up-state) in OAs. A slightly clearer peak in the mean-amplitude plots (**A** and **C**) was observed in the OA group relative to YAs, in both fixed- and adapted-band conditions.

Table S1

Sleep architecture of PSG screening night and between-group comparisons. N(YA) = 16; *n*(OA) = 16.

	YA	**OA**	**YA vs. OA**	
	M (SD)	**M (SD)**	***t* (df=30)**	***p***
Total Sleep Time (min)	411.06 (51.05)	384.41 (43.36)	1.59	.122
Sleep Efficiency (%)	88.81 (4.97)	82.48 (7.42)	2.833	.008
Sleep Onset Latency (min)	18.16 (18.37)	15.31 (19.99)	0.42	.678
N1 (% of sleep time)	9.21 (6.30)	17.98 (12.33)	-2.53	.017
N2 (% of sleep time)	50.45 (11.32)	48.31 (14.15)	0.47	.640
N3 (% of sleep time)	21.78 (12.61)	17.38 (7.73)	1.19	.243
REM (% of sleep time)	18.57 (4.83)	16.35 (4.40)	1.36	.185
N1 duration (min)	38.10 (27.16)	68.17 (41.13)	-2.43	.021
N2 duration (min)	210.11 (60.82)	186.77 (55.53)	1.14	.265
N3 duration (min)	85.57 (41.20)	66.48 (27.22)	1.57	.126
REM duration (min)	77.10 (23.83)	63.48 (20.12)	1.75	.091
Apnea-Hypopnea Index (AHI, /hr)	3.48 (2.22)	8.09 (3.41)	-4.52	.000

Note. YA, Young Adults; OA, Older Adults; N1, non-rapid-eye-movement (NREM) stage 1; N2, NREM stage 2; N3, NREM stage 3; REM, rapid-eye-movement sleep; WASO, wake after sleep onset; AHI, apnea-hypopnea index. *M*, mean; *SD*, standard deviation. Mins, minutes; hr, hour. Independent-samples *t*-tests indicate that, as expected, YA evidenced greater sleep efficiency, and OA evidenced a higher level of sleep apnea severity, and trends for higher levels (%, duration) of stage N1.

Table S2

Daily at-home sleep diary and actigraphy monitoring across the study interval. N(YA) = 16; *n*(OA) = 16.

	YA	OA	YA vs. OA	
	***M* (SD)**	***M* (SD)**	***t* (df=30)**	***p***
Sleep Diary				
# Days Recorded	16.75 (3.61)	15.69 (3.34)	0.87	.394
# of Naps[*]	2.38 (3.01)	3.94 (4.02)	-1.24	.223
Duration of Naps (min)	6.84 (8.09)	10.26 (12.15)	-0.94	.356
Lights Off Time[+*]	11 :40 (4 :12)	11 :28 (0 :52)	0.18	.859
Sleep Onset Latency (min)	12.10 (7.93)	12.46 (6.61)	-0.14	.890
Duration of WASO (min)	6.25 (4.61)	20.24 (15.61)	-3.44”	.003
Total Sleep Time (hrs)	7.52 (0.91)	6.77 (0.52)	2.84	.008
Wake up Time[+*]	8 :54 (3 :27)	6 :48 (0 :44)	2.14	.042
Sleep Efficiency (%)	90.81 (3.76)	84.58 (4.81)	4.09	.000
Sleep Quality	4.02 (0.48)	3.87 (0.56)	0.82	.416
Actigraphy				
# Days Recorded[++**]	11.93 (3.24)	12.43 (2.90)	-0.43	.669
Bed Time[++**]	9 :50 (7 :18)	11 :10 (0 :37)	-0.68”	.500
Sleep Onset Latency (min) [++**]	23.54 (11.62)	17.24 (10.21)	1.55	.134
Duration of WASO (min) [++**]	12.54 (8.89)	34.27 (33.58)	-2.42”	.033
Total time in Bed (hrs) [++**]	7:57:03 (0:56:31)	7:52:09 (0:32:55)	0.28	.779
Total Sleep Time (hrs) [++**]	6:52:50 (1:06:29)	6:37:13 (0:46:37)	0.73	.474
Wake up Time[++**]	8:10 (0:52)	7:02 (0:34)	4.07	.000
Sleep Efficiency (%)[++**]	86.24 (6.09)	84.56 (11.09)	0.51	.614

Note. YA, Young Adults; OA, Older Adults; WASO, wake after sleep onset; mins, minutes; Duration of naps shows group-level statistics only for those participants who reported naps. *M,* mean; *SD,* standard deviation. Min, minutes; hrs, hour. Sample size for actigraphy data was trimmed due to missing or corrupt data in YAs (+, *n* = 14, ++, *n* = 15) and in OAs (* *n* = 13; ** *n* = 14). ” non-equal variances.

Table S3

Event-detected NREM Slow Oscillations (0.5–1.25 Hz) on Cz between groups and across study nights. *n*(YA) = 16; *n*(OA) = 16.

	YA		**OA**		**YA vs. OA**		**EEGc vs. EEGm**	
	EEGc (*M*(SD))	**EEGm (*M*(SD))**	**EEGc (*M*(SD))**	**EEGm (*M*(SD))**	***F* (1, 28)**	***p***	***F* (1, 28)**	***p***
Count	1893.88 (433.28)	1962.81 (462.35)	1817.88 (429.50)	1832.25 (431.03)	0.577	.454	0.724	.402
Density (/30s)	3.27 (0.65)	3.26 (0.65)	3.25 (0.65)	3.18 (0.53)	0.067	.797	0.247	.623
Duration (s)	1.39 (0.05)	1.39 (0.05)	1.41 (0.07)	1.41 (0.06)	0.896	.352	0.951	.338
Peak-to-Peak (μV)	192.85 (41.29)	182.70 (37.85)	122.28 (31.40)	118.87 (27.06)	35.356	<.001	15.568	<.001
Energy ($\mu V^2 s$)	1399.58 (718.86)	1220.02 (625.45)	460.70^{+} (319.80)	426.04^{+} (256.98)	24.121	<.001	17.183	<.001
Peak Energy Freq (Hz)	0.72 (0.05)	0.71 (0.05)	0.69 (0.07)	0.69 (0.06)	1.192	.284	1.173	.288

Note. YA, Young Adults; OA, Older Adults; *M*, mean; SD, standard deviation. Freq, frequency. s, seconds; μV; microvolts; Hz, Hertz. *F*-statistic and *p*-values are for main effects of Group (YA vs. OA) and Night (EEGc vs. EEGm, repeated measure) in a 2x2 ANCOVA, controlling for age and sleep apnea severity. Covariates were mean-centered for each group separately. There was one noteworthy Group X Night trend interaction for SO energy ($F = 7.868$, $p = .009$), whereby the decrease seen in SO energy from the control night to the learning night was larger in YAs versus OAs. $^{+}$ denotes a significant Levene's test for equality of (error) variances across groups on a given night.

Table S4

Event-detected NREM sleep spindles on Cz using fixed bands (12–16 Hz) and adapted bands between groups and across study nights. n(YA) = 16; n(OA) = 16.

	YA		**OA**		**YA vs. OA**		**EEGc vs. EEGm**	
	EEGc (*M*(SD))	**EEGm (*M*(SD))**	**EEGc (*M*(SD))**	**EEGm (*M*(SD))**	***F* (1, 28)**	***p***	***F* (1, 28)**	***p***
				Fixed bands				
Count	961.75 (148.48)	1018.25 (153.74)	685.25 (177.24)	722.31 (170.79)	31.611	<.001	3.963	.056
Density (/30s)	1.66 (0.20)	1.70 (0.20)	1.23 (0.27)	1.27 (0.27)	27.278	<.001	5.938	.021
Duration (s)	0.78 (0.04)	0.78 (0.04)	0.72 (0.03)	0.72 (0.03)	30.647	<.001	0.144	.707
Peak-to-Peak (μV)	109.19 (17.88)	105.88 (15.80)	85.14 (18.72)	81.69 (16.40)	18.443	<.001	12.929	.001
Energy ($\mu V^2 s$)	162.51 (70.00)	162.25 (70.75)	103.24 (51.36)	104.45 (53.70)	7.289	.012	0.058	.812
Peak Energy Freq (Hz)	13.52 (0.45)	13.53 (0.46)	13.35 (0.30)	13.43 (0.33)	0.980	.331	2.471	.127
				Adapted bands				
Count	933.81 (175.86)	991.13 (168.05)	671.25 (151.47)	714.56 (157.86)	28.343	<.001	4.579	.041
Density (/30s)	1.61 (0.23)	1.65 (0.22)	1.20 (0.23)	1.25 (0.24)	24.674	<.001	8.218	.008
Duration (s)	0.78 (0.04)	0.78 (0.03)	0.72 (0.03)	0.72 (0.03)	22.659	<.001	0.018	.895
Peak-to-Peak (μV)	110.10 (18.54)	107.03 (16.10)	85.46 (18.32)	81.92 (15.99)	19.536	<.001	11.470	.002
Energy ($\mu V^2 s$)	161.69 (69.57)	161.80 (70.32)	102.59 (52.05)	103.19 (54.37)	7.341	.011	0.032	.858
Peak Energy Freq (Hz)	13.51 (0.51)	13.52 (0.51)	13.33 (0.37)	13.42 (0.39)	0.823	.372	2.996	.094

Note. YA, Young Adults; OA, Older Adults; *M*, mean; SD, standard deviation. Spindles detected using a fixed band (12–16 Hz) or using individually adapted bandwidths based on preliminary analysis of spectral

peaks (bandwidth = 4 Hz). Freq, frequency. s, seconds; μV; microvolts; Hz, Hertz. *F*-statistic and *p*-values are for main effects of Group (YA vs. OA) and Night (EEGc vs. EEGm, repeated measure) in a 2x2 ANCOVA, controlling for age and sleep apnea severity. Covariates were mean-centered for each group separately. There were no significant Group X Night interactions.

Table S5

MI and CP on Cz from NREM between study nights. n(YA) = 16; *n*(OA) = 16.

	MI		**CP**	
	EEGc (*M*(*SD*))	**EEGm (*M*(*SD*))**	**EEGc (*M*(*SD*))**	**EEGm (*M*(*SD*))**
			YA	
SO – σ (*f*)	-5.34 (1.03)	-4.90 (0.70)	16.65 (14.85)	18.54 (16.31)
SO – σ (*a*)	-5.45 (1.09)	-4.87 (0.78)	18.76 (15.74)	21.84 (14.95)
			OA	
SO – σ (*f*)	-5.24 (0.85)	-5.02 (1.12)	26.55 (17.20)	29.51 (23.77)
SO – σ (*a*)	-5.06 (0.68)	-4.92 (0.96)	25.87 (17.39)	28.13 (22.44)

Note. YA, Young Adults; OA, Older Adults; *M*, mean; *SD*, standard deviation. MI, log-transformed modulation index. SO, slow oscillation (0.5–1.25 Hz); σ *(f)*, sigma; fixed sigma band (12–16 Hz); σ *(a)*, adapted sigma band (bandwidth = 4 Hz). Pearson's correlations, examining the across-night stability of MI and CP from both fixed- and adapted-band conditions, revealed that MI was not correlated between nights in either group or condition (YA group: [MI (*f*): $r = -0.345$, $p = 0.191$; MI (*a*): $r = -0.436$, $p = 0.092$]; OA group: [MI (*f*): $r = 0.115$, $p = 0.673$; MI (*a*): $r = 0.104$, $p = 0.701$]). By contrast, CP was highly stable between nights in both groups and in each band-pair condition (YA group: [CP (*f*): $r = 0.914$, $p < 0.001$; CP (*a*): $r = 0.897$, $p < 0.001$], OA group: [CP (*f*): $r = 0.841$, $p < 0.001$; CP (*a*): $r = 0.840$, $p < 0.001$]).

Table S6

Between-group and across-night comparison of NREM SO-sigma MI and CP (fixed and adapted) on Cz separated by band-pair. n(YA) = 16; n(OA) = 16.

	Type III SS	df	Mean Square	*F*	*p*	Partial η^2
			MI			
SO – σ (*f*)						
Night (EEGc vs. EEGm)	1.688	1	1.688	1.903	.179	.064
Group (YA vs. OA)	0.002	1	0.002	0.003	.959	.000
Night X Age	3.562	1	3.562	4.015	.055	.125
Night X AHI	0.044	1	0.044	0.049	.826	.002
Group X Night	0.196	1	0.196	0.221	.642	.008
Error (Night)	24.843	28	0.887			
SO – σ (*a*)						
Night (EEGc vs. EEGm)	2.009	1	2.009	2.113	.157	.070
Group (YA vs. OA)	0.461	1	0.461	0.687	.414	.024
Night X Age	1.435	1	1.435	1.509	.230	.051
Night X AHI	0.090	1	0.090	0.095	.760	.003
Group X Night	0.773	1	0.773	0.813	.375	.028
Error (Night)	26.625	28	0.951			
			CP			
SO – σ (*f*)						
Night (EEGc vs. EEGm)	0.005	1	0.005	0.105	.749	.004
Group (YA vs. OA)	1.743	1	1.743	3.487	.072	.111
Night X Age	0.018	1	0.018	0.404	.530	.014
Night X AHI	0.017	1	0.017	0.369	.548	.013
Group X Night	0.004	1	0.004	0.092	.764	.003
Error (Night)	1.267	28	0.045			
SO – σ (*a*)						
Night (EEGc vs. EEGm)	0.139	1	0.139	2.689	.112	.088
Group (YA vs. OA)	0.261	1	0.261	1.015	.322	.035
Night X Age	0.123	1	0.123	2.372	.135	.078
Night X AHI	0.002	1	0.002	0.040	.842	.001
Group X Night	0.078	1	0.078	1.500	.231	.051
Error (Night)	1.450	28	0.052			

Note. SO, slow oscillation (0.5–1.25 Hz); σ *(f),* fixed sigma band (12–16 Hz); σ (*a*), adapted sigma (bandwidth = 4 Hz). MI, log-transformed modulation index. *F*-statistic and *p*-value are for the main effect of Night from a 2 (Night) x 2 (Group) ANCOVA, with control and learning nights as a repeated measure, controlling for age and sleep apnea severity. Values in **bold** denote results that reached or surpassed Bonferroni-adjusted *p*-value (.006). Values in *italics* denote a trend effect/marginal change at $p < .05$.

Table S7

Prediction of word-pair Overnight Consolidation by relative change between nights in SO-sigma MI and CP on Cz. n(YA) = 16; *n*(OA) = 16.

Band pair	**MI**					**CP**				
	F	**ΔR^2**	***B* (*SE*)**	***β***	***p***	***F***	**ΔR^2**	***B* (*SE*)**	***β***	***p***
YA										
SO – σ (*f*)	0.184	0.043	0.439 (0.596)	.213	.475	0.060	0.014	0.053 (0.128)	.120	.684
SO – σ (*a*)	0.316	0.073	0.514 (0.530)	.279	.351	0.164	0.039	0.094 (0.134)	.223	.500
OA										
SO – σ (*f*)	1.250	0.000	0.143 (1.687)	.030	.934	1.248	0.000	0.006 (0.131)	.013	.962*
SO – σ (*a*)	1.598	0.048	-1.645 (1.835)	-.285	.388	1.589	0.067	-0.306 (0.298)	-.291	.327

Note. YA, Young Adults; SO, slow oscillation (0.5–1.25 Hz); σ (*f*), fixed sigma band (12–16 Hz); σ *(a)*, adapted sigma band (bandwidth = 4 Hz). SO(+) – σ reflects SO events joined with a detected spindle; SO(+) – σ reflects SO events not joined with a detected spindle. MI, log-transformed modulation index. *F*-statistic, ΔR^2, *B (SE), β,* and *p*-value are hierarchical regression models (Model 2) with the MI value of interest as the independent variable predicting word-pair recall performance, controlling for age and sleep apnea severity. Values in **bold** denote results that reached or surpassed Bonferroni-adjusted *p*-value (.006). Values in *italics* denote a trend effect/marginal change at $p < .05$. *B*, unstandardized coefficient. *β*, standardized coefficient; ΔR^2, change in proportion of explained variance; *SE*, standard error. * outlier removed.

Table S8

Hierarchical regression to predict word-pair Consolidation Score by SO-sigma MI and CP interaction during the learning night, from Cz. n(YA) = 16; *n*(OA) = 16.

	YA						OA					
Band pair	***F* (df)**	***p***	**ΔR^2**	***B* (*SE*)**	***β***	***p*(*β*)**	***F* (df)**	***p***	**ΔR^2**	***B* (*SE*)**	***β***	***p*(*β*)**
SO – σ (*f*) (base)												
MI [a]	-		-	-0.909 (1.519)	-.215	.563	-		-	0.688 (1.861)	.120	.719
CP [a]	-		-	-0.029 (0.058)	-.160	.629	-		-	-0.080 (0.076)	-.296	.318
MI x CP	0.219 (5, 15)	.946	0.098	-0.102 (0.111)	-.327	.382	1.004 (5, 15)	.463	0.097	0.074 (0.089)	.241	.421
SO – σ (*a*) (base)												
MI [a]	-		-	-0.636 (1.192)	-.169	.605	-		-	-0.448 (2.579)	-.067	.866
CP [a]	-		-	-0.004 (0.061)	-.018	.954	-		-	-0.041 (0.088)	-.142	.654
MI x CP	0.515 (5, 15)	.760	0.204	-0.131 (0.084)	-.476	.152	0.718 (5, 15)	.625	0.027	0.000 (0.127)	.000	.999

Note. SO (0.5–1.25 Hz); σ (*f*), fixed sigma band (12–16 Hz); σ *(a)*, adapted sigma band (bandwidth = 4 Hz). MI, Modulation Index; CP, absolute coupling phase distance from the SO up-state. *F*-statistic, *p*-value, ΔR^2, *B (SE), β,* and *p*(*β*) are from hierarchical regression models to predict word-pair consolidation (Model 2) with centered MI and CP values alongside their interaction. Age and apnea-hypopnea index (measured on first (PSG) night) were entered in Model 1. *F*-statistic and ΔR^2 is presented only for the final model with interaction term. ΔR^2, change in proportion of explained variance; SE, standard error. *B*, unstandardized coefficient. *β*, standardized coefficient. *p*(*β*) is *p*-value associated with the standardized regression coefficient for the independent variable, controlling for other model predictors. Values in **bold** denote results that surpassed the conventional critical *p*-value (< .05). "(base)" refers to the baseline interaction model, containing two mean-centered predictors and their product as an interaction term; models in the two subsequent rows present follow-up analyses to examine moderating effects of MI when a significant interaction was found in the base model. [a], mean-centered main-effect predictor; [b], mean-centered moderator adjusted down by 1 SD-unit (i.e., lower MI); [c], main-centered moderator adjusted up by 1 SD-unit (i.e., higher MI).

Table S9

Descriptive counts and detection scores for slow oscillation sub-groups of overlapping SO-spindle events (SO+spindle) and isolated SO events (SO-spindle) across groups and nights, by channel, with fixed-band detected spindles. n(YA) = 16; n(OA) = 16..

	YA		**OA**		**YA vs. OA**		**EEGc vs. EEGm**	
	EEGc (*M*(SD)), [Min-Max]	**EEGm (*M*(SD)), [Min-Max]**	**EEGc (*M*(SD)), [Min-Max]**	**EEGm (*M*(SD)), [Min-Max]**	***F* (1, 28)**	***p***	***F* (1, 28)**	***p***
Channel Fz								
SO + Spindle								
Count	170.63 (41.83) [92-254]	193.69 (53.65) [121-342]	207.19 (93.96) [50-429]	210.06 (73.24) [91-361]	1.380	.250	2.308	.140
Density (/30s)	0.30 (0.07) [0.17-0.38]	0.33 (0.09) [0.21-0.50]	0.37 (0.15) [0.10-0.64]	0.36 (0.11) [0.19-0.64]	2.160	.153	1.445	.239
F1 Ratio	0.13 (0.03) [0.09-0.18]	0.14 (0.03) [0.10-0.20]	0.15 (0.04) [0.10-0.25]	0.16 (0.03) [0.10-0.21]	3.170	.086	2.955	.097
SO – Spindle								
Count	1763.06 (422.58) [912-2499]	1833.94 (443.47) [1034-2658]	1736.06 (379.92) [915-2236]	1768.31 (382.78) [1087-2318]	0.137	.714	0.971	.333
Density (/30s)	3.03 (0.61) [1.67-4.01]	3.04 (0.61) [1.79-3.89]	3.11 (0.58) [1.77-3.96]	3.08 (0.47) [2.09-3.85]	0.080	.779	0.017	.896
Channel Cz								
SO + Spindle								
Count	146.44 (29.09) [99-219]	160.81 (42.77) [94-234]	138.81 (50.81) [46-216]	138.81 (39.72) [61-204]	1.111	.301	2.337	.138
Density (/30s)	0.26 (0.07) [0.17-0.41]	0.27 (0.08) [0.16-0.44]	0.25 (0.08) [0.10-0.36]	0.24 (0.06) [0.13-0.34]	0.687	.414	0.276	.603
F1 Ratio	0.11 (0.02) [0.07-0.15]	0.11 (0.02) [0.07-0.15]	0.10 (0.03) [0.06-0.16]	0.10 (0.02) [0.07-0.15]	0.424	.520	2.949	.097
SO – Spindle								

Count	1747.69 (424.28) [1080-2636]	1802.31 (446.01) [1017-2725]	1679.19 (399.91) [811-2265]	1693.81 (408.83) [990-2360]	0.463	.502	0.574	.455
Density (/30s)	3.01 (0.61) [1.98-4.23]	2.99 (0.61) [1.76-3.98]	3.00 (0.62) [1.57-3.77]	2.94 (0.52) [1.84-3.64]	0.026	.874	0.343	.563

Note. *M*, mean; *SD*, standard deviation. SO + Spindle reflects SO events that are joined in time with a detected sleep spindle (minimum 25% overlap between events), and SO – Spindle reflects SO events not joined with a sleep spindle. Spindles detected using a fixed band (9–13 Hz [Fz], 12–16 Hz [Cz]). F1 Ratio reflects the accuracy of detecting overlapping SO and spindle events and distinguishing these from isolated SO events without an overlapping spindle; F1 is calculated as the harmonic mean of scores reflecting precision (ratio of true positive hits:[true positives + false positives]) and recall (ratio of true positives:[true positives + false negatives]). In this context, an F1 score of 1 indicates that every SO overlapped with a spindle, and likewise every spindle overlapped with a SO. *F*-statistic and *p*-value are for the main effect of Night from a 2 (Night) x 2 (Group) ANCOVA, with control and learning nights as a repeated measure, controlling for age and sleep apnea severity. Pearson's correlations revealed highly stable values for SO(+) F1 scores between nights (YA: [Fz: $r = 0.778$, $p \leq 0.001$; Cz: $r = 0.911$, $p \leq 0.001$], OA: [Fz: $r = 0.878$, $p \leq 0.001$; Cz: $r = 0.846$, $p \leq 0.001$]).

Table S10

Descriptive counts and detection scores for slow oscillation sub-groups of overlapping SO-spindle events (SO+spindle) and isolated SO events (SO-spindle) across groups and nights, by channel, with adapted-band detected spindles. n(YA) = 16; *n*(OA) = 16..

	YA		OA		YA vs. OA		EEGc vs. EEGm	
	EEGc (*M*(SD)), [Min-Max]	**EEGm (*M*(SD)), [Min-Max]**	**EEGc (*M*(SD)), [Min-Max]**	**EEGm (*M*(SD)), [Min-Max]**	***F* (1, 28)**	***p***	***F* (1, 28)**	***p***
Channel Fz								
SO + Spindle								
Count	163.19 (36.90) [85-262]	181.38 (36.14) [126-249]	193.75 (92.46) [60-399]	198.00 (68.91) [104-348]	1.328	.259	1.748	.197
Density (/30s)	0.28 (0.06) [0.16-0.37]	0.31 (0.08) [0.20-0.47]	0.34 (0.15) [0.12-0.64]	0.34 (0.11) [0.22-0.61]	1.894	.180	1.023	.321
F1 Ratio	0.13 (0.03) [0.09-0.18]	0.14 (0.04) [0.09-0.19]	0.14 (0.04) [0.09-0.23]	0.15 (0.03) [0.10-0.20]	1.596	.217	2.353	.136
SO – Spindle								
Count	1769.88 (428.79) [918-2584]	1846.44 (463.74) [1043-2848]	1750.69 (386.84) [906-2249]	1781.50 (380.24) [1074-2331]	0.108	.745	1.034	.318
Density (/30s)	3.05 (0.62) [1.68-4.15]	3.06 (0.63) [1.80-4.16]	3.13 (0.59) [1.75-4.01]	3.10 (0.46) [2.16-3.81]	0.107	.746	0.013	.912
Channel Cz								
SO + Spindle								
Count	141.69 (29.73) [96-219]	157.81 (40.79) [96-235]	137.50 (50.04) [43-219]	139.38 (41.55) [61-213]	0.645	.429	3.892	.058
Density (/30s)	0.25 (0.07) [0.17-0.40]	0.27 (0.08) [0.17-0.44]	0.24 (0.08) [0.09-0.35]	0.24 (0.06) [0.13-0.34]	0.357	.555	0.911	.348
F1 Ratio	0.10 (0.02) [0.07-0.15]	0.11 (0.02) [0.07-0.15]	0.10 (0.03) [0.06-0.17]	0.10 (0.02) [0.07-0.15]	0.286	.597	2.229	.147
SO – Spindle								

Count	1752.25 (426.40) [1083-2638]	1804.88 (451.71) [1013-2726]	1680.06 (399.26) [815-2263]	1692.88 (406.26) [990-2363]	0.500	.485	0.499	.486
Density (/30s)	3.02 (0.62) [1.98-4.23]	3.00 (0.62) [1.75-3.99]	3.00 (0.62) [1.58-3.76]	2.94 (0.51) [1.84-3.62]	0.037	.849	0.401	.532

Note. *M*, mean; *SD*, standard deviation. SO + Spindle and SO – Spindle is as defined in Table S9 (above). Spindles detected using individually adapted bandwidths based on preliminary analysis of spectral peaks (bandwidth = 4 Hz). F1 Ratio reflects the accuracy of detecting overlapping SO and spindle events and distinguishing these from isolated SO events without an overlapping spindle; F1 is calculated as the harmonic mean of scores reflecting precision (ratio of true positive hits:[true positives + false positives]) and recall (ratio of true positives:[true positives + false negatives]). In this context, an F1 score of 1 indicates that every SO overlapped with a spindle, and likewise every spindle overlapped with a SO. *F*-statistic and *p*-value are for the main effect of Night from a 2 (Night) x 2 (Group) ANCOVA, with control and learning nights as a repeated measure, controlling for age and sleep apnea severity. Pearson's correlations revealed highly stable values for SO(+) F1 scores between nights (YA: [Fz: $r = 0.724$, $p = 0.002$; Cz: $r = 0.901$, $p \leq 0.001$], OA: [Fz: $r = 0.846$, $p \leq 0.001$; Cz: $r = 0.814$, $p \leq 0.001$]).

Table S11

MI and CP from SO sub-group events across groups and between study nights. *n*(YA) = 16; *n*(OA) = 16.

	MI		**CP**	
	EEGc (*M*(*SD*))	**EEGm (*M*(*SD*))**	**EEGc (*M*(*SD*))**	**EEGm (*M*(*SD*))**
		Channel Fz		
		YA		
SO(+) – σ (*f*)	-6.68 (0.72)	-6.81 (0.61)*	110.86 (14.95)	127.66 (38.75)***
SO(-) – σ (*f*)	-5.56 (0.92)	-5.39 (0.58)	102.14 (24.80)	107.87 (26.94)***
SO(+) – σ (*a*)	-6.89 (0.80)	-6.82 (0.68)***	89.91 (53.77)	95.81 (57.76)***
SO(-) – σ (*a*)	-5.04 (1.02)	-5.48 (0.79)	80.28 (38.48)	87.70 (40.39)***
		OA		
SO(+) – σ (*f*)	-7.10 (0.75)	-6.97 (0.72)*	64.88 (54.48)	81.43 (53.73)**
SO(-) – σ (*f*)	-6.11 (0.75)	-6.36 (0.46)*	65.31 (19.10)	63.11 (18.27)***
SO(+) – σ (*a*)	-6.63 (0.98)	-6.69 (0.85)**	72.07 (57.83)	82.01 (60.27)***
SO(-) – σ (*a*)	-5.80 (0.84)	-5.67 (0.76)	75.71 (40.04)	75.66 (37.72)***
		Channel Cz		
		YA		
SO(+) – σ (*f*)	-6.10 (0.83)	-6.10 (0.95)***	15.99 (14.94)	13.19 (12.29)*
SO(-) – σ (*f*)	-5.63 (0.93)	-5.79 (1.02)*	20.37 (17.46)	24.39 (17.46)***
SO(+) – σ (*a*)	-6.15 (0.81)	-6.07 (0.96)***	15.13 (12.22)	14.02 (8.84)**
SO(-) – σ (*a*)	-5.72 (0.82)	-5.60 (0.90)	23.08 (17.84)	26.85 (15.18)***
		OA		
SO(+) – σ (*f*)	-5.71 (0.64)	-5.56 (0.39)**	30.33 (19.87)	32.19 (22.64)***
SO(-) – σ (*f*)	-5.19 (1.12)	-5.55 (0.90)	25.06 (15.23)	28.44 (24.82)**
SO(+) – σ (*a*)	-5.71 (0.76)	-5.68 (0.56)***	31.42 (24.21)	30.29 (22.17)**
SO(-) – σ (*a*)	-5.26 (0.90)	-5.31 (0.81)	24.74 (15.40)	27.49 (23.16)**

Note. YA, Young Adults; OA, Older Adults; *M,* mean, *SD,* standard deviation; MI, log-transformed modulation index; CP, coupling phase distance from the SO up-state. SO, slow oscillation (0.5–1.25 Hz); σ (*f*), fixed sigma band (9–13 Hz [Fz], 12–16 Hz [Cz]); σ *(a)*, adapted sigma band (bandwidth = 4 Hz). SO(+) – σ reflects SO events joined with a detected spindle; SO(+) – σ reflects SO events not joined with a detected spindle. There was a mix of significant and non-significant correlations for MI between nights in each group and on each channel, which is unlike analyses above on Fz and Cz from all SO events, where MI was not correlated between nights. Like analyses with all SO events, CP variables evidenced a

significant (positive) correlation between nights in each group and on each channel. *, significance of across-night Pearson's correlation in each group at $p < .05$; **, $p < .01$; ***, $p < .001$.

Table S12

Between-group and across-night comparison of SO-sigma MI from SO sub-group events (fixed and adapted bands) on Fz, separated by band-pair. n(YA) = 16; n(OA) = 16.

	Type III SS	df	Mean Square	*F*	*p*	Partial η^2
SO(+) – σ (*f*) MI						
Night (EEGc vs. EEGm)	<0.001	1	<0.001	0.000	.995	.000
Group (YA vs. OA)	1.353	1	1.353	2.182	.151	.072
Night X Age	*1.056*	*1*	*1.056*	*5.942*	*.021*	*.175*
Night X AHI	0.328	1	0.328	1.845	.185	.062
Group X Night	0.291	1	0.291	1.640	.211	.055
Error (Night)	4.976	28	0.178			
SO(-) – σ (*f*) MI *						
Night (EEGc vs. EEGm)	0.033	1	0.033	0.089	.768	.003
Group (YA vs. OA)	**9.096**	**1**	**9.096**	**13.641**	**.001**	**.336**
Night X Age	0.300	1	0.300	0.793	.381	.029
Night X AHI	0.003	1	0.003	0.007	.932	.000
Group X Night	0.742	1	0.742	1.962	.173	.068
Error (Night)	10.205	27	0.378			
SO(+) – σ (*a*) MI						
Night (EEGc vs. EEGm)	0.001	1	0.001	0.005	.942	.000
Group (YA vs. OA)	0.542	1	0.542	0.552	.464	.019
Night X Age	0.309	1	0.309	1.721	.200	.058
Night X AHI	0.073	1	0.073	0.406	.529	.014
Group X Night	0.044	1	0.044	0.244	.625	.009
Error (Night)	5.024	28	0.179			
SO(-) – σ (*a*) MI						
Night (EEGc vs. EEGm)	0.405	1	0.405	0.516	.479	.018
Group (YA vs. OA)	*3.614*	*1*	*3.614*	*5.123*	*.032*	*.155*
Night X Age	0.042	1	0.042	0.054	.819	.002
Night X AHI	0.274	1	0.274	0.350	.559	.012
Group X Night	1.278	1	1.278	1.628	.212	.055
Error (Night)	21.980	28	0.785			

Note. YA, Young Adults; OA, Older Adults. SO, slow oscillation (0.5–1.25 Hz); σ (*f),* fixed sigma band (9–13 Hz); (*a)*, adapted sigma (bandwidth = 4 Hz). SO(+) – σ reflects SO events joined with a detected spindle; SO(+) – σ reflects SO events not joined with a detected spindle; MI, log-transformed modulation index. *F*-statistic and *p*-value are for the main effect of Night from a 2 (Night) x 2 (Group) ANCOVA, with control and learning nights as a repeated measure, controlling for age and sleep apnea severity. Values in **bold** denote results that reached or surpassed Bonferroni-adjusted *p*-value (.006). Values in *italics* denote a trend effect/marginal change at $p < .05$. * outlier removed.

Table S13

Between-group and across-night comparison of SO-sigma from SO sub-group events (fixed and adapted bands) on Cz, separated by band-pair. n(YA) = 16; *n*(OA) = 16.

	Type III SS	df	Mean Square	*F*	*p*	Partial η^2
SO(+) – σ (*f*) MI						
Night (EEGc vs. EEGm)	0.097	1	0.097	1.278	.268	.044
Group (YA vs. OA)	3.366	1	3.366	3.287	.081	.105
Night X Age	0.066	1	0.066	0.873	.358	.030
Night X AHI	0.001	1	0.001	0.009	.924	.000
Group X Night	0.089	1	0.089	1.173	.288	.040
Error (Night)	2.120	28	0.076			
SO(-) – σ (*f*) MI						
Night (EEGc vs. EEGm)	1.118	1	1.118	1.626	.213	.055
Group (YA vs. OA)	1.898	1	1.898	1.470	.235	.050
Night X Age	2.219	1	2.219	3.227	.083	.103
Night X AHI	2.606	1	2.606	3.790	.062	.119
Group X Night	0.156	1	0.156	0.227	.638	.008
Error (Night)	19.249	28	0.687			
SO(+) – σ (*a*) MI						
Night (EEGc vs. EEGm)	0.044	1	0.044	0.360	.553	.013
Group (YA vs. OA)	2.762	1	2.762	2.455	.128	.081
Night X Age	0.045	1	0.045	0.368	.549	.013
Night X AHI	0.046	1	0.046	0.382	.541	.013
Group X Night	0.008	1	0.008	0.064	.802	.002
Error (Night)	3.402	28	0.121			
SO(-) – σ (*a*) MI						
Night (EEGc vs. EEGm)	0.020	1	0.020	0.028	.869	.001
Group (YA vs. OA)	2.194	1	2.194	2.752	.108	.089
Night X Age	0.631	1	0.631	0.902	.350	.031
Night X AHI	0.181	1	0.181	0.258	.616	.009
Group X Night	0.128	1	0.128	0.182	.673	.006
Error (Night)	19.608	28	0.700			

Note. YA, Young Adults; OA, Older Adults. SO, slow oscillation (0.5–1.25 Hz); σ (*f),* fixed sigma band (12–16 Hz); (*a)*, adapted sigma (bandwidth = 4 Hz). SO(+) – σ reflects SO events joined with a detected spindle; SO(+) – σ reflects SO events not joined with a detected spindle; MI, log-transformed modulation index. *F*-statistic and *p*-value are for the main effect of Night from a 2 (Night) x 2 (Group) ANCOVA, with control and learning nights as a repeated measure, controlling for age and sleep apnea severity. Values in **bold** denote results that reached or surpassed Bonferroni-adjusted *p*-value (.006). Values in *italics* denote a trend effect/marginal change at $p < .05$. * outlier removed.

Table S14

Between-group and across-night comparison of SO-sigma CP from SO sub-group events (fixed and adapted bands) on Fz, separated by band-pair. n(YA) = 16; *n*(OA) = 16.

	Type III SS	df	Mean Square	*F*	*p*	Partial η^2
SO(+) – σ (*f*) CP						
Night (EEGc vs. EEGm)	0.274	1	0.274	3.424	.075	.109
Group (YA vs. OA)	*1.349*	*1*	*1.349*	*4.567*	*.041*	*.140*
Night X Age	0.000	1	0.000	0.006	.941	.000
Night X AHI	0.011	1	0.011	0.133	.718	.005
Group X Night	0.017	1	0.017	0.214	.647	.008
Error (Night)	2.239	28	0.080			
SO(-) – σ (*f*) CP *						
Night (EEGc vs. EEGm)	<0.001	1	<0.001	0.000	.986	.000
Group (YA vs. OA)	**0.764**	**1**	**0.764**	**26.466**	**<.001**	**.495**
Night X Age	<0.001	1	<0.001	0.005	.942	.000
Night X AHI	0.000	1	0.000	0.074	.788	.003
Group X Night	0.008	1	0.008	1.279	.268	.045
Error (Night)	0.173	27	0.006			
SO(+) – σ (*a*) CP						
Night (EEGc vs. EEGm)	0.029	1	0.029	1.278	.268	.044
Group (YA vs. OA)	0.234	1	0.234	0.579	.453	.020
Night X Age	0.000	1	0.000	0.007	.933	.000
Night X AHI	0.025	1	0.025	1.102	.303	.038
Group X Night	0.027	1	0.027	1.190	.285	.041
Error (Night)	0.626	28	0.022			
SO(-) – σ (*a*) CP						
Night (EEGc vs. EEGm)	0.021	1	0.021	3.397	.076	.108
Group (YA vs. OA)	0.063	1	0.063	0.497	.486	.017
Night X Age	<0.001	1	<0.001	0.003	.958	.000
Night X AHI	0.001	1	0.001	0.168	.685	.006
Group X Night	0.003	1	0.003	0.430	.517	.015
Error (Night)	0.171	28	0.006			

Note. SO(+) – σ reflects SO events joined with a detected spindle; SO(+) – σ reflects SO events not joined with a detected spindle; σ (*f),* fixed sigma band (9–13 Hz); (*a)*, adapted sigma (bandwidth = 4 Hz). *F*-statistic and *p*-value are for the main effect of Night from a 2 (Night) x 2 (Group) ANCOVA, with control and learning nights as a repeated measure, controlling for age and sleep apnea severity. Values in **bold** denote results that reached or surpassed Bonferroni-adjusted *p*-value (.006). Values in *italics* denote a trend effect/marginal change at $p < .05$. * outlier removed.

Table S15

Between-group and across-night comparison of NREM SO-sigma CP from SO sub-group events (fixed and adapted bands) on Cz, separated by band-pair. n(YA) = 16; n(OA) = 16.

	Type III SS	df	Mean Square	*F*	*p*	Partial η^2
SO(+) – σ (*f*) CP						
Night (EEGc vs. EEGm)	0.025	1	0.025	0.264	.611	.009
Group (YA vs. OA)	*2.640*	*1*	*2.640*	*8.385*	*.007*	*.230*
Night X Age	0.026	1	0.026	0.281	.600	.010
Night X AHI	0.064	1	0.064	0.685	.415	.024
Group X Night	0.051	1	0.051	0.549	.465	.019
Error (Night)	2.615	28	0.093			
SO(-) – σ (*f*) CP						
Night (EEGc vs. EEGm)	0.091	1	0.091	1.184	.286	.041
Group (YA vs. OA)	0.158	1	0.158	0.472	.498	.017
Night X Age	0.030	1	0.030	0.392	.536	.014
Night X AHI	0.024	1	0.024	0.318	.577	.011
Group X Night	0.205	1	0.205	2.286	.112	.088
Error (Night)	2.141	28	0.076			
SO(+) – σ (*a*) CP						
Night (EEGc vs. EEGm)	0.034	1	0.034	0.352	.558	.012
Group (YA vs. OA)	*1.585*	*1*	*1.585*	*6.137*	*.020*	*.180*
Night X Age	0.092	1	0.092	0.950	.338	.033
Night X AHI	0.003	1	0.003	0.028	.869	.001
Group X Night	0.018	1	0.018	0.182	.673	.006
Error (Night)	2.712	28	0.097			
SO(-) – σ (*a*) CP						
Night (EEGc vs. EEGm)	0.153	1	0.153	3.779	.062	.119
Group (YA vs. OA)	0.023	1	0.023	0.060	.808	.002
Night X Age	0.072	1	0.072	1.778	.193	.060
Night X AHI	0.000	1	0.000	0.005	.943	.000
Group X Night	0.093	1	0.093	2.301	.140	.076
Error (Night)	1.133	28	0.040			

Note. SO(+) – σ reflects SO events joined with a detected spindle; SO(+) – σ reflects SO events not joined with a detected spindle; σ (*f),* fixed sigma band (12–16 Hz); (*a)*, adapted sigma (bandwidth = 4 Hz). *F*-statistic and *p*-value are for the main effect of Night from a 2 (Night) x 2 (Group) ANCOVA, with control and learning nights as a repeated measure, controlling for age and sleep apnea severity. Values in **bold** denote results that reached or surpassed Bonferroni-adjusted *p*-value (.006). Values in *italics* denote a trend effect/marginal change at $p < .05$.

Table S16

Prediction of word-pair Overnight Consolidation by relative change between nights in SO-sigma MI from SO sub-group events (fixed and adapted bands) on Fz and Cz. n(YA) = 16; *n*(OA) = 16.

Band pair	Fz					Cz				
	F	**ΔR^2**	***B* (*SE*)**	***β***	***p***	***F***	**ΔR^2**	***B* (*SE*)**	***β***	***p***
YA										
SO(+) – σ (*f*) MI	0.340	0.078	-1.888 (1.878)	-.397	.334	0.191	0.045	2.027 (2.694)	.226	.466
SO(-) – σ (*f*) MI	0.205	0.048	-0.664 (0.852)	-.225	.451	0.088	0.021	0.465 (0.918)	.149	.622
SO(+) – σ (*a*) MI	0.065	0.015	-0.918 (2.123)	-.130	.673	0.037	0.009	-0.577 (1.782)	-.100	.752
SO(-) – σ (*a*) MI	0.163	0.039	-0.421 (0.607)	-.197	.501	0.010	0.002	-0.142 (0.918)	-.051	.879
OA										
SO(+) – σ (*f*) MI	1.350	0.015	-1.283 (2.635)	-.132	.635	1.284	0.005	-1.141 (3.886)	-.076	.774
SO(-) – σ (*f*) MI	1.250	0.001	0.167 (1.841)	.024	.929	1.921	0.087	-1.574 (1.267)	-.363	.238
SO(+) – σ (*a*) MI	1.308	0.009	-0.870 (2.325)	-.099	.715*	1.296	0.007	-1.394 (4.159)	-.098	.743
SO(-) – σ (*a*) MI	1.648	0.054	1.471 (1.535)	.236	.357	1.248	0.000	0.073 (1.431)	.014	.960

Note. YA, Young Adults; SO, slow oscillation (0.5–1.25 Hz); σ (*f*), fixed sigma band (9–13 Hz [Fz], 12–16 Hz [Cz]); σ *(a)*, adapted sigma band (bandwidth = 4 Hz). SO(+) – σ reflects SO events joined with a detected spindle; SO(+) – σ reflects SO events not joined with a detected spindle. MI, log-transformed modulation index. *F*-statistic, ΔR^2, *B (SE), β,* and *p*-value are hierarchical regression models (Model 2) with the MI value of interest as the independent variable predicting word-pair recall performance, controlling for age and sleep apnea severity. *B*, unstandardized coefficient. *β*, standardized coefficient; ΔR^2, change in proportion of explained variance; *SE*, standard error. * outlier removed.

Table S17

Prediction of word-pair Overnight Consolidation by relative change between nights in SO-sigma CP from SO sub-group events (fixed and adapted bands) on Fz and Cz. n(YA) = 16; *n*(OA) = 16.

Band pair	Fz					Cz				
	F	**ΔR^2**	***B* (*SE*)**	***β***	***p***	***F***	**ΔR^2**	***B* (*SE*)**	***β***	***p***
YA										
SO(+) – σ (*f*) CP	0.394	0.089	-0.034 (0.031)	-.321	.300	1.575	0.282	0.152 (0.070)	.682	.051
SO(-) – σ (*f*) CP	0.130	0.031	-0.035 (0.057)	-.203	.548	0.274	0.064	0.107 (0.118)	.260	.385
SO(+) – σ (*a*) CP	0.490	0.109	0.037 (0.031)	.341	.250	1.010	0.201	0.174 (0.100)	.513	.107
SO(-) – σ (*a*) CP	0.131	0.031	-0.044 (0.071)	-.204	.546	0.067	0.016	0.046 (0.105)	.145	.668
OA										
SO(+) – σ (*f*) CP	1.595	0.047	0.035 (0.039)	.235	.389	1.247	0.000	0.004 (0.131)	.009	.974
SO(-) – σ (*f*) CP	1.550	0.042	0.088 (0.106)	.210	.421	1.283	0.005	-0.029 (0.102)	-.076	.779
SO(+) – σ (*a*) CP	1.353	0.015	-0.031 (0.063)	-.143	.630	1.247	0.000	-0.001 (0.090)	-.003	.992
SO(-) – σ (*a*) CP	1.317	0.010	-0.058 (0.144)	-.101	.696	2.653	0.184	-0.345 (0.185)	-.448	.088*

Note. YA, Young Adults; SO, slow oscillation (0.5–1.25 Hz); σ (*f*), fixed sigma band (9–13 Hz [Fz], 12–16 Hz [Cz]); σ *(a)*, adapted sigma band (bandwidth = 4 Hz). SO(+) – σ reflects SO events joined with a detected spindle; SO(+) – σ reflects SO events not joined with a detected spindle. *F*-statistic, ΔR^2, *B (SE), β,* and *p*-value are hierarchical regression models (Model 2) with the MI value of interest as the independent variable predicting word-pair recall performance, controlling for age and sleep apnea severity. *B*, unstandardized coefficient. *β*, standardized coefficient; ΔR^2, change in proportion of explained variance; *SE*, standard error. * outlier removed.

Table S18

Comparison of raw coupling phase from analyses with all SO events (fixed and adapted bands) between experimental nights on Fz and Cz. n(YA) = 16; *n*(OA) = 16.

	EEGc				EEGm					
	Angle	*R*	*Z*	*p(Z)*	Angle	*R*	*Z*	*p(Z)*	***F***	***p(F)***
Channel Fz										
YA										
SO – σ (*f*)	0.33	0.16	53.69	<.001	0.45	0.16	55.74	.002	0.096	.293
SO – σ (*a*)	-0.09	0.16	56.77	<.001	-0.06	0.17	58.27	<.001	0.087	.621
OA										
SO – σ (*f*)	-0.33	0.17	63.18	<.001	-0.34	0.18	65.62	<.001	2.44E-06	.996
SO – σ (*a*)	-0.30	0.21	102.48	<.001	-0.32	0.22	102.81	<.001	7.35E-05	.950
Channel Cz										
YA										
SO – σ (*f*)	-1.32	0.19	71.71	<.001	-1.26	0.19	85.04	<.001	0.021	.694
SO – σ (*a*)	-1.26	0.20	75.38	<.001	-1.22	0.20	87.65	<.001	0.032	.663
OA										
SO – σ (*f*)	-1.95	0.21	85.23	<.001	-2.04	0.21	86.82	<.001	0.161	.339
SO – σ (*a*)	-1.95	0.21	84.48	<.001	-2.01	0.21	86.81	<.001	0.147	.363

Note. YA, Young Adults; OA, Older Adults; CP, coupling phase; SO, slow oscillation (0.5–1.25 Hz); σ (*f*), fixed sigma band (9–13 Hz [Fz], 12–16 Hz [Cz]); σ *(a)*, adapted sigma band (bandwidth = 4 Hz). *Angle* and *R* are the direction and magnitude of the resultant vector of the coupling phase distribution. *Z*-statistic and associated *p*-value are for the Rayleigh test for non-uniformity of a circular distribution. *F*-statistic and associated *p*-value are for the Watson-Williams test for unequal means in circular distributions. Because this last test assumes unimodal distributions, it was only conducted if the Rayleigh tests were significant only for fixed-band measures in both age groups. There were no differences in coupling phase between nights.

Table S19

Comparison of raw coupling phase from SO sub-group events (fixed and adapted bands) between experimental nights on Fz and Cz. n(YA) = 16; n(OA) = 16.

	EEGc				EEGm					
	Angle	*R*	*Z*	*p(Z)*	Angle	*R*	*Z*	*p(Z)*	***F***	***p(F)***
Channel Fz										
YA										
SO(+) – σ (*f*)	1.19	0.21	8.51	.04	1.52	0.19	8.84	.082	N/A	N/A
SO(-) – σ (*f*)	0.26	0.16	48.48	<.001	0.36	0.17	53.20	<.001	0.097	.434
SO(+) – σ (*a*)	-0.35	0.21	9.51	.169	0.75	0.18	6.53	.069	N/A	N/A
SO(-) – σ (*a*)	-0.10	0.16	50.94	<.001	0.04	0.17	54.53	<.001	0.056	.497
OA										
SO(+) – σ (*f*)	-0.27	0.19	8.29	.088	0.49	0.17	7.91	.187	N/A	N/A
SO(-) – σ (*f*)	-0.30	0.17	55.39	<.001	-0.32	0.18	57.21	<.001	0.037	.601
SO(+) – σ (*a*)	-0.22	0.22	13.63	.134	-0.23	0.23	14.01	.076	N/A	N/A
SO(-) – σ (*a*)	-0.29	0.21	87.61	<.001	-0.31	0.22	88.54	<.001	0.005	.696
Channel Cz										
YA										
SO(+) – σ (*f*)	-1.53	0.37	21.41	<.001	-1.60	0.37	26.15	.006	0.150	.584
SO(-) – σ (*f*)	-1.22	0.17	55.31	<.001	-1.15	0.18	65.48	<.001	0.006	.826
SO(+) – σ (*a*)	-1.52	0.37	20.36	.004	-1.58	0.35	22.97	.008	0.749	.346

SO(-) – σ (*a*)	-1.17	0.18	59.45	<.001	-1.13	0.19	68.52	<.001	0.014	.772
OA										
SO(+) – σ (*f*)	-2.09	0.37	22.35	<.001	-2.13	0.41	25.28	.016	0.163	.465
SO(-) – σ (*f*)	-1.87	0.19	65.26	<.001	-1.99	0.19	64.58	<.001	0.182	.332
SO(+) – σ (*a*)	-1.73	0.38	21.43	.002	-2.07	0.40	23.43	.015	0.030	.753
SO(-) – σ (*a*)	-1.87	0.19	65.95	<.001	1.96	0.19	65.77	<.001	0.168	.370

Note. YA, Young Adults; OA, Older Adults; CP, coupling phase; SO(+) – σ reflects SO events joined with a detected spindle; SO(+) – σ reflects SO events not joined with a detected spindle; σ (*f*), fixed sigma band (9–13 Hz [Fz], 12–16 Hz [Cz]); σ *(a)*, adapted sigma band (bandwidth = 4 Hz). *Angle* and *R* are the direction and magnitude of the resultant vector of the coupling phase distribution. *Z*-statistic and associated *p*-value are for the Rayleigh test for non-uniformity of a circular distribution. *F*-statistic and associated *p*-value are for the Watson-Williams test for unequal means in circular distributions. Values in **bold** denote results that reached or surpassed Bonferroni-adjusted *p*-value (.006). Values in *italics* denote a trend effect/marginal change at $p < .05$. Because this last test assumes unimodal distributions, it was only conducted if the Rayleigh tests were significant for measures using fixed bands, both for SO(+) – σ (*f*) and SO(+) – σ (*f*). Conversely, Rayleigh tests for measures using adapted bands were significant only for SO(+) – σ (*a*).

Table S20

Circular-linear correlations between word-pair Overnight Consolidation with SO-sigma (SO – σ) raw coupling phase on EEGm (learning) night on Fz and Cz. n(YA) = 16; n(OA) = 16.

	Fz				**Cz**			
	YA		**OA**		**YA**		**OA**	
	r	***p***	***r***	***p***	***r***	***p***	***r***	***p***
SO-sigma CP (all SO events)								
SO – σ (*f*)	0.224	.669	0.337	.403	0.198	.731	0.394	.289
SO – σ (*a*)	0.205	.715	0.389	.299	0.273	.552	0.260	.583
SO-sigma CP (SO+spindle events vs SO-spindle events)								
SO(+) – σ (*f*)	0.198	.730	0.348	.379	0.443	.208	0.612	.050
SO(-) – σ (*f*)	0.247	.615	0.335	.409	0.278	.538	0.408	.264
SO(+) – σ (*a*)	0.048	.982	0.533	.103	0.395	.286	*0.724*	*.015*
SO(-) – σ (*a*)	0.341	.395	0.398	.282	0.521	.114	0.205	.715

Note. YA, Young Adults; OA, Older Adults; CP, coupling phase; SO, slow oscillation (0.5–1.25 Hz); σ (*f*), fixed sigma band (9–13 Hz [Fz], 12–16 Hz [Cz]); σ *(a)*, adapted sigma band (bandwidth = 4 Hz). SO(+) – σ reflects SO events joined with a detected spindle; SO(+) – σ reflects SO events not joined with a detected spindle. Coupling phase correlations are circular-circular to account for the distribution of phases around the unit circle. Values in **bold** denote results that reached or surpassed Bonferroni-adjusted p-value (.006). Values in *italics* denote a trend effect/marginal change at $p < .05$.

Table S21

Power spectral density (PSD) from NREM sleep (average of all cycles) between study nights on Fz and Cz. n(YA) = 16; n(OA) = 16.

	YA		OA	
	EEGc (*M*(SD))	**EEGm (*M*(SD))**	**EEGc (*M*(SD))**	**EEGm (*M*(SD))**
			Channel Fz	
SO (μV^2)	4.98 (0.50)	4.91 (0.48)	4.11 (0.60)	4.03 (0.54)
σ (*f*) (μV^2)	2.45 (1.10)	2.55 (1.06)	1.32 (2.67)	1.26 (2.60)
σ (*a*) (μV^2)	2.14 (1.58)	2.27 (1.50)	1.69 (3.34)	1.62 (3.20)
			Channel Cz	
SO (μV^2)	4.73 (0.45)	4.63 (0.43)	3.96 (0.56)	3.89 (0.49)
σ (*f*) (μV^2)	0.53 (1.52)	0.51 (1.54)	-1.42 (1.92)	-1.44 (1.98)
σ (*a*) (μV^2)	0.92 (1.32)	0.90 (1.37)	-1.18 (1.80)	-1.20 (1.86)

Note. YA, Young Adults; OA, Older Adults; SO, Slow Oscillation power (0.5–1.25 Hz); σ (*f*), fixed sigma band (9–13 Hz [Fz], 12–16 Hz [Cz]); σ *(a)*, adapted sigma band (bandwidth = 4 Hz). *M*, mean; *SD*, standard deviation. μV; microvolts. Values in the upper portion of each cell reflect PSD in absolute (μV^2) units, and in the lower portion of each cell reflect PSD after normalizing to a pre-sleep quiet/resting period. *, $p < .05$ and **, $p < .01$ from independent samples *t*-tests for differences in average PSD from each measure between groups on each study night. There were no significant between-night differences found on any PSD measure when measured within each group separately.

Table S22

Between-group and across-night comparison of NREM SO and sigma (fixed and adapted bands) power spectral density (PSD) on Fz and Cz. n(YA) = 16; *n*(OA) = 16.

	Type III SS	df	Mean Square	*F*	*p*	Partial η^2
			Channel Fz			
SO (μV^2)						
Night (EEGc vs. EEGm)	0.037	1	0.037	2.619	.117	.086
Group (YA vs. OA)	0.990	1	0.990	2.134	.155	.071
Night X Age	0.017	1	0.017	1.181	.286	.040
Night X AHI	0.012	1	0.012	0.871	.359	.030
Group X Night	0.024	1	0.024	1.734	.199	.058
Error (Night)	0.392	28	0.014			
σ (*f*) (μV^2)						
Night (EEGc vs. EEGm)	0.256	1	0.256	2.681	.113	.087
Group (YA vs. OA)	*43.568*	*1*	*43.568*	*7.403*	*.011*	*.209*
Night X Age	0.165	1	0.165	1.733	.199	.058
Night X AHI	0.174	1	0.174	1.826	.187	.061
Group X Night	0.321	1	0.321	3.365	.077	.107
Error (Night)	2.670	28	0.095			
σ (*a*) (μV^2)						
Night (EEGc vs. EEGm)	0.383	1	0.383	3.464	.073	.110
Group (YA vs. OA)	48.315	1	48.315	4.125	.052	.128
Night X Age	0.282	1	0.282	2.548	.122	.083
Night X AHI	0.144	1	0.144	1.304	.263	.045
Group X Night	*0.493*	*1*	*0.493*	*4.466*	*.044*	*.138*
Error (Night)	3.094	28	0.110			
			Channel Cz			
SO (μV^2)						
Night (EEGc vs. EEGm)	0.031	1	0.031	2.404	.132	.079
Group (YA vs. OA)	0.832	1	0.832	2.145	.154	.071
Night X Age	0.012	1	0.012	0.912	.348	.032
Night X AHI	0.015	1	0.015	1.189	.285	.041

Group X Night	0.015	1	0.015	1.158	.291	.040
Error (Night)	0.363	28	0.013			
σ (*f*) (μV^2)						
Night (EEGc vs. EEGm)	0.015	1	0.015	0.226	.638	.008
Group (YA vs. OA)	18.336	1	18.336	3.671	.066	.116
Night X Age	0.024	1	0.024	0.381	.542	.013
Night X AHI	0.016	1	0.016	0.256	.617	.009
Group X Night	0.018	1	0.018	0.274	.605	.010
Error (Night)	1.798	28	0.064			
σ (*a*) (μV^2)						
Night (EEGc vs. EEGm)	0.020	1	0.020	0.322	.575	.011
Group (YA vs. OA)	14.691	1	14.691	3.601	.068	.114
Night X Age	0.031	1	0.031	0.502	.484	.018
Night X AHI	0.014	1	0.014	0.228	.637	.008
Group X Night	0.025	1	0.025	0.393	.536	.014
Error (Night)	1.747	28	0.062			

Note. YA, Young Adults; OA, Older Adults; SO, Slow Oscillation power (0.5–1.25 Hz); σ (*f*), fixed sigma band (9–13 Hz [Fz], 12–16 Hz [Cz]); σ *(a)*, adapted sigma band (bandwidth = 4 Hz). μV; microvolts; *F*-statistic and *p*-value are for the main effect of Night from a 2 (Night) x 2 (Group) ANCOVA, with control and learning nights as a repeated measure, controlling for age and sleep apnea severity. # Greenhouse-Geisser corrected. Values in **bold** denote results that reached or surpassed Bonferroni-adjusted *p*-value (.006). Values in *italics* denote a trend effect/marginal change at $p < .05$.

Table S23

Prediction of word-pair Overnight Consolidation by relative change between nights in power spectral density (PSD) on Fz and Cz. n(YA) = 15; *n*(OA) = 12.

	YA					**OA**				
	***F* (3, 12)**	**ΔR^2**	***B* (*SE*)**	***β***	***p***	***F* (3, 12)**	**ΔR^2**	***B* (*SE*)**	***β***	***p***
Channel Fz										
Learning task night (EEGm)										
SO (μV^2)	1.520	0.275	-3.575 (1.676)	-.583	.054	2.840	0.178	5.656 (2.963)	.473	.080
σ (*f*) (μV^2)	0.121	0.029	-0.484 (0.811)	-.175	.562	1.388	0.020	0.431 (0.757)	.174	.579
σ (*a*) (μV^2)	0.101	0.024	-0.318 (0.584)	-.162	.596	1.267	0.003	-0.122 (0.565)	-.061	.832
PSD change between nights (EEGm – EEGc)										
SO (μV^2)	*2.072*	*0.341*	*11.589 (4.652)*	*.586*	*.028*	1.284	0.005	2.753 (9.358)	.080	.774
σ (*f*) (μV^2)	0.169	0.040	2.373 (3.357)	.206	.493	1.247	0.000	-0.038 (3.012)	-.004	.990
σ (*a*) (μV^2)	0.015	0.003	0.463 (2.386)	.058	.849	1.256	0.001	0.450 (3.035)	.041	.885
Channel Cz										
Learning task night (EEGm)										
SO (μV^2)	0.293	0.068	-2.109 (2.258)	-.307	.369	*3.711*	*0.244*	*7.206 (3.036)*	*.543*	*.035*
σ (*f*) (μV^2)	0.017	0.004	0.121 (0.573)	.063	.836	*4.804*	*0.308*	*2.225 (0.780)*	*.685*	*.015*
σ (*a*) (μV^2)	0.006	0.001	-0.070 (0.633)	-.032	.914	2.256	0.123	1.559 (1.026)	.450	.155
PSD change between nights (EEGm – EEGc)										
SO (μV^2)	*2.725*	*0.405*	*12.241 (4.284)*	*.656*	*.014*	1.247	0.000	-0.236 (10.393)	-.006	.982

σ (*f*) (μV^2)	0.100	0.024	1.265 (2.336)	.158	.598	1.272	0.004	-1.201 (4.972)	-.061	.813
σ (*a*) (μV^2)	0.148	0.035	1.669 (2.526)	.192	.521	1.286	0.006	-1.395 (4.665)	-.076	.770

Note. YA, Young Adults; OA, Older Adults; SO, Slow Oscillation power (0.5–1.25 Hz); σ (*f*), fixed sigma band (9–13 Hz [Fz], 12–16 Hz [Cz]); σ *(a)*, adapted sigma band (bandwidth = 4 Hz). μV; microvolts. *F*-statistic, ΔR^2, *B (SE), β,* and *p*-value are for hierarchical regression models (Model 2) with the PSD measure of interest as the independent variable, controlling for age and sleep apnea severity. Values in **bold** denote results that reached or surpassed Bonferroni-adjusted *p*-value (.006). Values in *italics* denote a trend effect/marginal change at $p < .05$. *B*, unstandardized coefficient. *β*, standardized coefficient; ΔR^2, change in proportion of explained variance; *SE*, standard error.

General Discussion

The overarching aim of my research was to examine measures of cross-frequency coupling (CFC) during NREM sleep and assess their relations with learning and overnight declarative memory consolidation in healthy ageing. Results from my two studies add to a growing but mixed literature on the subject. First, this research adds mixed support for the hypotheses that coupled brain activity during NREM sleep in older adults is 1) responsive to pre-sleep declarative learning, 2) associated with overnight memory consolidation, and 3) evidences an age-related decline compared to younger adults. Chiefly, across both included studies, the main CFC measures did not evidence a significant difference from a baseline/control after pre-sleep learning at the group-level, in either older or younger sample. Relations between CFC and memory, and the largest age-group differences, were mainly centered on measures of coupling phase distance (CP) rather than coupling strength (MI). Second, this research adds to the complexity of our understanding about this neural activity and what it represents by highlighting methodological and contextual nuances about how SO – σ CFC is measured and relates to cognition.

In the following sections I will first summarize the main findings of my two studies and draw comparisons between them. I will then integrate and synthesize my research with other related studies and expand on my discussion about the methodological nuances involved in this research. Following this is a broader discussion about our growing conceptual understanding behind the intersection of coupled brain activity during sleep, memory consolidation, and ageing. Finally, I will highlight specific implications of this research, and identify some potentially important future directions and analyses of interest.

Summary of Results from each Study

The aim of my first study was to examine SO – σ CFC during NREM (N2+N3) sleep and its association with learning and declarative memory in a sample of healthy older adults who completed a two-night protocol. This study did not find evidence of a learning effect on SO – σ CFC, as both measures of coupling strength (via MI) and coupling phase distance from the up-state (CP) were stable across the two study nights. This study also demonstrated that none of the MI measures (main or supplemental analyses) were associated with memory on their own, but that a CP closer to the up-state after learning

was associated with better memory consolidation; this was the case for measures from all SO events, and from SO(-) events in the supplemental analyses. Moreover, the results of an exploratory interaction model were interpreted to suggest that relations between frontal CP and memory consolidation may be enhanced when accompanied by higher versus lower coupling strength.

The primary goal of my second study was to repeat the Study 1 analyses with an independent sample of older adults (OA) as well as a young adult (YA) control group, and in a better-controlled, 3-night study protocol with counterbalanced experimental and control task nights. This new protocol enhanced our methodological control over the analyses and addressed important limitations of Study 1. Study 2 results showed that MI exhibited a trend-level increase in YAs versus OAs in our main analysis (Fz, all SO events), with a significant MI difference only in our supplemental analyses with isolated SO (SO(-)) events. Regarding CP, a significant group difference was observed in our primary (Fz, all SOs) and supplemental analyses (Fz, SO(-) events); coupling phase distance was locked later in the up-to-down-state transition phase among YAs compared to OAs, whose coupling phase was locked earlier in the same phase. Supplemental analyses on Cz also revealed the typical coupling pattern of fast spindle power peaking during or after the up-state in YAs, but earlier in the down-to-up-state transition in OAs, however the group difference fell shy of our corrected significance level. Of note, group differences were found only among measures derived using a fixed-frequency bandwidth for all subjects. Contrary to expectation, there were no main effects of Night across any measure, and contrary to the results of Study 1, there were also no significant associations with memory consolidation in either group. One exception was of a trend-level correlation in OAs for raw SO(+) – σ (*a*) coupling phase with memory consolidation, in support of fast spindle coupling phase later in the rising SO phase and closer to (but not after) the peak.

Synthesis of Findings and Integration with Similar Studies

Overall, Study 1 offered novel results to suggest that coupled brain activity with slow (but not fast) spindle power may be associated with overnight memory consolidation in OAs. In turn, results of Study 1 were interpreted as supporting a hypothesis that coupled brain activity continues to be associated with memory consolidation even in older age. As for Study 2, I offered empirical support for age-group

differences in SO – σ CP in the slow spindle range, although there were no significant associations with memory in either YA or OA group. Older adults in both of my studies evidenced greater fast spindle activity during the rising SO phase, before the up-state peak; by contrast, there was greater representation of slow spindle activity shortly after the up-state in OAs, which differed from YAs in my Study 2. Both findings are in-line with previous works that show an age-related shift, or "de-coupling", between SO and spindle activity in OAs versus YAs (Helfrich et al., 2018; Ladenbauer et al., 2021; Muehlroth et al., 2019). However, Schneider and colleagues (2020) did not find a prominent de-coupling of SO and fast spindle (12–15 Hz) activity between a young adult and middle-aged cohort (*M* (*SD*) age = 55.7 (1.0) years). Of note, the mean sample age in Schneider's study was more than a decade younger than in the studies of Helfrich et al. (2017; ~73 years old), Muehlroth et al. (2019; ~68 years old), Ladenbauer et al (2021; ~66 years old) and in my two studies (Study 1: ~69 years old; Study 2: ~67 years old). The notion that group differences would be more apparent with greater age is intuitive, and in-line with a recent study (Djonlagic et al., 2021) showing declines in coupled brain activity across the 50th to 90th decade. It is also important to recall that OAs in my Study 1 had more severe sleep apnea relative to OAs in my Study 2, potentially reflecting differences in "brain age" versus "chronological age" in my two studies.

The largest coupling differences between younger and older groups are often found with (centro-parietal) fast spindle activity. Helfrich et al. (2018) noted the strongest differences in fast spindle coupling phase patterns over fronto-central recording sites, while Muehlroth et al. (2019) reported age-group differences in slow spindle coupling phase across both frontal and central sites, and Ladenbauer et al. (2021) noted group differences (in slow and fast spindle CFC) only on a centro-parietal region of interest. My Study 2 did not replicate the more central topography in age-group differences of fast-spindle CFC; instead, I showed that group differences were strongest for measures of slow spindle CP on Fz, both in my main (all SO events) and supplemental analyses (SO(-) events). One key difference in the Ladenbauer study is that they collected data during a daytime nap, while the other studies (including mine) examined overnight sleep. Chiefly, this speaks to the potential circadian effects of measuring oscillation activity and CFC during daytime versus nighttime sleep periods (e.g., different proportions of SWS).

Helfrich et al. (2018) reported that (central) SO-fast-spindle coupling strength was higher in YAs versus OAs, whereas Ladenbauer et al (2021) reported no major group differences in coupling strength. My study, by contrast, found evidence for greater slow spindle coupling strength in YAs only in supplemental analyses of Fz SO(-) events. Thus, evidence remains mixed regarding age-group differences in measures of coupling strength. One major difference between studies is that the analyses in my study and in Ladenbauer et al. (2021) used data from a total NREM sleep period, while Helfrich et al. (2018) examined only periods of SWS. Given the known differences in SO and spindle activity between N2 and N3 sleep (Cox et al., 2017 and 2018; Djonlagic et al., 2021; Fernandez & Lüthi, 2020; Menicucci et al., 2009), age-group differences in coupling strength may become clearer when examining only deep SWS. However, and also important to note, Helfrich et al. (2018) examined only one night of data, and their study included a pre-sleep learning task of 120 word-nonsense word pairs that were trained to a 100% criterion; even though their study did not find a correlation between MI and recognition memory, the impact of the intensive learning period both on post-learning sleep depth and oscillation activity may be a factor. As discussed, my Study 2 analyses may have been too underpowered to detect more significant effects; yet, with the smaller sample size in mind, it was intriguing that an age-group effect was still detectable for MI with slow spindle power on the frontal channel.

Previous studies with just younger or more middle-aged adults (e.g., Mikutta et al., 2019; Mölle et al., 2009, 2011; Mylonas et al., 2020; Ngo et al., 2013; Niknazar et al., 2015; Perrault et al., 2019; Ruch et al., 2012; Schreiner et al., 2021; Zhang et al., 2020) paint a generally consistent picture that fast spindle coupling with the SO up-state facilitates declarative memory consolidation. More precise SO – σ CFC has also been associated with better memory in studies with older adults (Helfrich et al., 2018; Muehlroth et al., 2019), and particularly with fast spindle activity. Drawing from the results of a large epidemiological study of CFC in older adults (Djonlagic et al., 2021), the fast spindle coupling phase among OAs in my two studies may have been too mis-timed with the SO up-state (i.e., too early) to evidence the predicted associations with memory. Given the contemporary emphasis on the role of fast spindle coupling, it was interesting that my Study 1 (Weiner et al., 2023) found evidence for relations with memory in the context

of slow spindle coupling (i.e., peaking closer to the up-state). By contrast, Muehlroth et al. (2019) reported that more slow-spindle coupling with the up-state (reflecting a more "aged" pattern) was associated with worse memory. There are noteworthy similarities between their study and mine, including the focus on N2+N3 sleep, an overlapping slow spindle band (them: 9–12.5 Hz; mine: 9–13 Hz), and using an episodic (associative) memory task. However, Muehlroth et al. (2019) exposed OAs to a memory test with 280 scene-word pairs, compared to the 40 word-pairs used here, and their memory scores were based on a combination of recognition memory (remember/forget) and recall memory (select the second letter of the correct word), compared to the more standard cued-recall paradigm in my study. Thus, our testing protocols were quite different, which may at least partially contextualize the divergent findings. In turn, additional research will be needed to develop a more fine-tuned understanding about NREM SO-slow-spindle coupling in relation to memory and ageing.

Multiple related studies that I've mentioned in this thesis have found a stronger association with declarative memory for measures of coupling phase compared to measures of coupling strength. More often, coupling strength is associated with performance on non-declarative/procedural tasks (e.g., Bartsch et al., 2019; Mikutta et al., 2019; however, see Demanuele et al., 2017) compared to declarative memory tasks (Helfrich et al., 2018; Mikutta et al., 2019; Niknazar et al., 2015; Zhang et al., 2020; however, see Hahn et al., 2020). A noteworthy exception is from Dehnavi et al. (2021), who reported evidence that stronger SO-slow-spindle coupling strength (near the SO trough) during a baseline was positively correlated with stimulation-associated improvements in word-pair overnight retention, while SO-fast-spindle coupling strength (near the SO peak) correlated with improvements on a figural-paired associates task. The "active systems" model of memory consolidation suggests that a HC-neocortical dialogue during sleep is reflected by the triple-phase-locking of SO, spindle, and ripple activity. In turn, perhaps the brain activity inferred by measures of coupling strength are not reflective of a similar HC-neocortical dialogue, and thus does not contribute in the same way to a "corticalization" process of HC engrams.

Collectively, we are seeing more and more evidence that SO – σ CFC declines with greater age; however, there is less consistent evidence for where in the brain these age differences most often occur,

when they occur (e.g., between N2 and N3 stages), and how these changes may be associated with impaired overnight memory consolidation. The differences in methodology noted so far between my and previous studies in younger versus older adults are highly relevant when drawing comparisons between the reported findings. Of note, the review above is by no means exhaustive, and it highlighted only a selection of differences across the noted studies that may help contextualize my findings. My thesis highlighted several methodological decisions that were made during this research, and there are a multitude of other method-related factors that come into play when examining CFC.

Importance of Methodology and Signal Processing Decisions

The study of brain oscillations in general, and of cross-frequency coupling more specifically, requires a multitude of pre-processing and analysis steps that require thoughtful consideration. In the process of addressing the goals and questions of my research, I was also able to highlight the sensitivity of CFC measures to their analytical context, and to even small changes in the analysis pipeline (see Cox & Fell, 2020 for an important discussion on this topic). Several methodological routes were considered in the planning of these dissertation studies, and the analyses themselves followed an ever-developing pipeline of signal filtering and processing. There was considerable overlap in the approach and analyses across my two studies, however there were also distinctions in the methods and analysis both within (e.g., across main and supplemental sections), and between each study that are important to consider. A selection of these methodological distinctions and nuances are discussed briefly below.

Examining all SO Events Versus SO Sub-Groups

Findings from my main and supplemental analyses in both studies highlight the potential advantage of examining SO – σ CFC with naturally co-occurring events. Specifically, in Study 1 I interpreted the primary effect between CP closer to the up-state and better memory consolidation as being driven by coupling with SO events that did not overlap with a spindle (SO(-)). In Study 2, there was greater signal for CFC group differences when examining SO sub-groups, and a (trend-level) correlation between SO(+) – σ coupling phase and memory. There may be functional differences between coupling derived from SO(+) events compared to SO(-) events, as demonstrated here, and as suggested by others

(e.g., Djonlagic et al., 2021; Hahn et al., 2020; Klinzing et al., 2016; Muehlroth et al., 2019; Niknazar et al., 2015; Schreiner et al., 2021). SO-spindle complexes have been associated with increased power of HC ripples in rats (Oyanedel et al., 2020), and with overnight memory consolidation in humans (e.g., Helfrich et al., 2019; Hahn et al., 2020; Schneider et al., 2021). Schreiner and colleagues (2021) suggested that SO-spindle complexes may help tune the target cortical area for synaptic plasticity and memory reprocessing during an ensuing spindle refractory period). Both of my studies with older adults, by contrast, suggest stronger effects with coupling on frontal SO(-) events in relation to memory (Study 1) and to declines with age (Study 2). Of note, Schreiner et al. (2021), Helfrich et al. (2018), and Hahn et al. (2020) each examined faster spindle activity on a central recording site, and the latter two studies both focused their analyses on SWS.

Methodologically, examining CFC on overlapping SO-spindle complexes helps ensure genuine rises in power among *both* the phase-giving (SO) and amplitude-giving (spindle) signals (c.f., Aru et al., 2015). However, examining SO-spindle complexes could increase variability of coupling dynamics in a sample, given the variability across subjects in the timing of sleep spindles (vs. sigma power) to the SO phase, especially across distinct (e.g., frontal vs. central) recording sites (Ngo et al., 2020). Importantly, many previous studies of SO+spindle CFC have anchored their coupling analyses to a particular phase of the SO (e.g., up-state or down-state peak), whereas my study detected complexes when events satisfied a general overlap criteria of at least 25%. Ultimately, the presence or absence of a spindle could reasonably alter estimates of SO – σ CFC (e.g., potential impact on background sigma activity), and in turn cloud detection of effects if not properly accounted for (e.g., by examining SO(+) and SO(-) events separately).

Individualized Versus Fixed Spindle Frequency Bands

Available studies are mixed in their use of fixed versus individually adapted frequency bands for SO – σ CFC analysis, with more recent studies appearing to move towards the use of individually adapted bands (e.g., based on spectral peaks, as in my Study 2; Cox et al., 2018; Dehnavi et al., 2021; Hahn et al., 2020). The use of adapted bands is in-line with current knowledge about individual differences in spindle characteristics and topography ("spindle fingerprint"; Bódizs et al., 2009; Cox et al., 2017; Eggert et al.,

2015; Fernandez & Lüthi, 2020; Ujma et al., 2015), and with spindles evidencing strong intra-individual, but not inter-individual, night-to-night consistency (Eggert et al., 2015). In turn, use of adapted bands may optimize spindle detection (Ujma et al., 2015). It is possible this holds true as well for coupled spindle/sigma activity. Indeed, a longitudinal study in children and youth (Hahn et al., 2020) showed that coupling strength was more strongly related to memory performance in the context of adapted- relative to fixed-band measures. Given the variability of within-person trajectories for age-related changes in sleep oscillations (c.f., Muehlroth et al., 2019; Muehlroth, Rasch, & Werkle-Bergner, 2020), accounting for individual brain activity differences when examining CFC may be important when studying older adults.

Main and supplemental analyses from Study 2 highlight distinctions in CFC derived using a fixed versus individually adapted sigma bandwidth. Unsurprisingly, there was greater variability in coupling among the adapted-band (vs. fixed-band) analyses, such that the standard error of amplitude increases across each SO phase bin was higher, and the raw coupling phase was more spread out and overlapping across the two groups; these differences between fixed- and adapted-band conditions were more evident on measures from Fz, suggesting that individual differences may be clearer for CFC with slower spindle activity. Nevertheless, group differences were minimal among the adapted-band analyses. This observation resonates strongly with results described by Muehlroth & Werkle-Bergner (2020), where age-group differences in detected SO activity were stronger when detections were run using a fixed, compared to an adapted, amplitude threshold. Thus, a potential consequence of examining CFC with fixed bands is that this could perhaps exaggerate ageing-related differences that may otherwise not be present or may be much more subtle when accounting for variation in brain activity. In turn, deriving CFC with adapted bands may better capture inter-subject variability that is lost when all participants are treated the same. At the same time, there may be something unique about coupled brain activity within specific frequency ranges (i.e., those used in our fixed-band analyses) that are not captured when spindle frequency is allowed to vary across subjects. Accordingly, more research is needed to better determine how much of an advantage is gained when examining CFC with fixed versus adapted frequency bands, and perhaps if each method is better suited for a specific purpose.

Measures of Relative Change Between Nights

Study 1 provided evidence that a shift in SO-slow-spindle CP towards the up-state after learning is associated with better memory consolidation. By contrast, Study 2 did not find a similar association in an independent sample. Potentially interesting associations can be gleaned by measuring change in a metric between conditions rather than focusing solely on a raw comparison of one condition to the other. For example, Papalambros et al. (2017) showed that change in SWA was more strongly associated with memory performance in an older sample (60-84 years old), compared to SWA from an experimental and control condition considered separately. Beyond the influence of lower statistical power in Study 2, it is interesting to also consider the effects of our two protocols in explaining the divergent findings. Chiefly, Study 1 examined change in CFC after a learning task from a non-learning baseline night, where the learning task was always given on Night 2; conversely, Study 2 examined coupling change between a counterbalanced learning task and non-learning control task. One interpretation is that memory associations with relative (within-person) shifts in CFC dynamics are clearer when the opposing condition contains no task, whereas relations with change are obscured when both conditions include a cognitively engaging task. This further speaks to the benefits of repeating this study both with a larger sample, and with a protocol that includes 4 visits and 3 experimental nights, with one of the experimental nights containing no task (e.g., see Dehnavi et al., 2021).

SO Detection and CFC Signal-Analysis

Both studies in this dissertation used an SO event detector based on the algorithm described by Staresina et al. (2015). This detector selected only the largest slow waves detected for each individual and each recording. However, certain differences can be noticed in the SO parameters between studies, which may be due to seemingly small updates in the SO filtering steps between Study 1 and Study 2. As well, both studies examined measures of coupling strength and coupling phase on these detected events. However, whereas coupling phase metrics and circular statistics were computed similarly across the studies, the calculation of MI was adjusted for Study 2 following developments in our pipeline. Specifically, the SO events in Study 1 were concatenated (i.e., stitched together) before computing the

modulation index from phase-amplitude dynamics across the signal, while in Study 2 the MI was computed from each detected SO individually before deriving a grand-average MI. Despite the same general pattern of no significant change in MI between nights in either study, coupling strength values were noticeably larger in Study 2 versus Study 1; as well, in Study 1 the measures of MI were strongly correlated between nights, whereas in Study 2 this was only the case for MI values from SO sub-groups (e.g., SO(+) events). It is possible that both observations could be attributed to a statistical consequence of deriving coupling strength as an average of a concatenated SO signal (Study 1) compared to a grand average MI across each SO event separately (Study 2).

The divergent observations between studies emphasizes the importance of methodology in examining both SO events and CFC, highlighting the sensitivity of coupling metrics to small adjustments in the signal analysis pipeline. These observations strongly resonate with the commentary of Cox and Fell (2020), who demonstrated the sometimes large effects of even minor changes to signal normalization, montage choice, oscillation filtering, surrogate testing, and other factors; chiefly, the authors suggest that each step in an analysis pipeline be checked before proceeding to the next step (i.e., to ensure/not assume that the pipeline is correctly analyzing data in the expected ways). Analytic standards for CFC studies have not yet been established (although, see Aru et al., 2015), however several papers offer guidelines and caveats about measurement of CFC from oscillatory signals. For example, cautionary notes have been given about the consequences of using frequency bandwidths that are too narrow and capture only activity around a peak (Hyafil, 2015), not accounting for the influence of higher harmonics from slower-frequency oscillations (Jensen et al., 2016), and detecting modulated oscillations within cognitively or behaviourally meaningful time scales (Dvorak & Fenton, 2014). Such sensitivity to analytical decisions is highly important for researchers to consider in future studies of NREM coupling, particularly in the context of ageing, and especially when attempting to replicate previous findings.

Significance of Research: Theoretical Considerations and Contributions

The “active systems” model suggests that memory consolidation during NREM sleep occurs through a “HC-neocortical dialogue” orchestrated by precisely timed interactions between HC, TC, and

cortical brain regions (Klinzing et al., 2019). This model posits that overnight memory consolidation is facilitated or optimized when memory representations (both from the HC and neocortex) are co-reactivated during moments when cortical synaptic changes (e.g., long-term potentiation) are more likely to occur (i.e., during a period of mass cortical excitability; Geva-Sagiv & Nir, 2019; Helfrich et al., 2019). Coupled brain activity is thus thought to facilitate the "corticalization" of temporary HC engrams into more permanent neocortical representations through, for example, gist abstraction and integration into longer-term associative networks (Alger et al., 2014; Gibson et al., 2022). Current thinking is that spindles, particularly fast spindles, may be a stronger mediator of memory transfer between HC and cortical sites (Clemens et al., 2011; Rosanova & Ulrich, 2005), perhaps through facilitating a burst-pattern expression of ripple activity that helps grow new neural connections (e.g., see Jiang et all., 2019b).

In agreement with Muehlroth and colleagues (Muehlroth et al., 2019; Muehlroth, Rasch, & Werkle-Bergner, 2020), ageing-related declines in SO activity may disrupt or impair the normal HC-neocortical "dialogue" during sleep, and these declines in CFC may be associated with deficits in memory consolidation. One mechanistic explanation for this could relate to distinctions between SO and delta waves. For instance, a recent optogenetic study showed that disrupting SOs increased the propensity for spindles to couple with delta wave up-states, while disrupting delta waves resulted in more spindles coupled to the SO (Kim et al., 2019). Extending this to CFC in ageing, it is possible that natural declines in SO activity with age coincide with an increased representation of delta waves, resulting in poorer integration of memory representations from the HC (coupled to spindle oscillations), and in turn, poorer memory consolidation (i.e., greater propensity towards forgetting; c.f., Schneider et al., 2020). Thus, impaired NREM CFC may be both a consequence of ageing (e.g., from reduced sleep depth and stability, and/or declines in cortical volume), and a potential mechanism of impaired memory consolidation.

Results of this dissertation are consistent with previous studies in showing the typical patterns of coupling dynamics reported between the SO phase with fast spindle activity (earlier in the rising SO phase in OAs vs. YAs) and slow spindle activity (earlier in the up-to-down-state transition in OAs vs. YAs). The current work is novel in highlighting the potential associations between overnight memory

consolidation and coupling with slow spindle activity in OAs (Study 1), and showcasing both an age-related difference in slow spindle coupling phase patterns as well as the blurring of these age differences after accounting for individual differences (Study 2). These results together could be interpreted as suggesting that coupling with slower spindle activity may play a larger role in sleep-associated memory processes than previously thought, at least in older adults, that effects may be specifically influenced by the presence or absence of a sleep spindle in the analyzed signal, and that ageing-related declines in NREM coupling may be stronger or clearer in the context of SO-slow-spindle coupling.

Expanding the Conceptual Lens

This dissertation provided novel evidence to support the potential role of SO-slow-spindle CFC in overnight memory consolidation in older adults, when similar effects were not seen among CFC measures with fast spindle activity. As well, nuanced distinctions were drawn when examining CFC on SO(+) and SO(-) sub-group events. The "active systems consolidation" model particularly emphasizes the memory-associated benefits of coupling with fast spindle activity near the up-state, whereas the role of slow spindle coupling is less clear and less often discussed. However, considering together the results of my Study 1 (SO-slow spindle CP near the up-state correlated with better word-pair memory) and my Study 2 (age-group differences in SO-slow-spindle CFC), alongside other SO – σ CFC studies in older adults (e.g., Dehnavi et al., 2021; Helfrich et al., 2018, Muehlroth et al., 2019), overnight memory consolidation may perhaps depend on the coordination and timing between coupling with both fast spindle (near the peak) *and* slow spindle activity (near the trough), and these dynamics may shift with greater age.

A Case for Theta Activity during NREM Sleep

It is conceivable too that interactions between SOs, spindles, and ripples do not tell the full story about neural dynamics of overnight memory consolidation. Accordingly, recent studies have illuminated the potential added role of theta activity and theta phase-coupling during NREM sleep in facilitating neural communication. Gonzalez and colleagues (2018) demonstrated that theta bursts (TBs; 5–8 Hz), identified in the cortex and thalamus, reliably preceded cortical down-states tied to the SO. Unlike spindles, TBs were not temporally correlated between cortical and temporal regions, and TBs showed

unique phase relations with high-gamma activity (60–100 Hz). Theta modulation within the SO frequency has been demonstrated elsewhere as well (Cox et al., 2020; Jiang et al., 2019a and 2019b; Schreiner et al., 2018), and it has been proposed that TBs may initiate the down-state→ripple→spindle→up-state sequence. The relative influence of theta activity within the intersection of NREM CFC, memory, and ageing has not been studied as much yet compared to the coupling between SO and spindle activity. Although, Schriener and colleagues (2018) showed, in young adults, that cue-triggered 5-Hz theta frequency patterns during sleep emerged at a rate of ~1 Hz. It remains to be established if theta oscillations are similarly coupled to the SO in scalp-measured EEG based on measures of coupling strength and coupling phase, and if theta-coupling is also associated with memory consolidation. However, two studies have both demonstrated a distinction in their analyses between SO coupling with theta activity and slow spindle activity (e.g., based on power increases during the SO [Klinzing et al., 2016] and correlations with memory performance [Dehnavi et al., 2021]).

Theta may be a relevant to overnight memory consolidation because theta activity is proposed to serve similar mnemonic functions between awake and asleep states. A recent study (Gibson et al., 2022) showed that theta power at encoding interacted with post-learning spindle density in predicting word recognition performance, and more specifically related to theme recognition and memory generalization. As suggested by studies with direct measures of intracranial EEG (Gonzalez et al., 2018) and indirect measures of scalp EEG (Clouter et al., 2017; Schriener et al., 2018), TBs during sleep may (re-)organize cortical information before the down-state to help identify related HC traces for relay to the cortex during the up-state. Theta may thus act as a mediator between the neocortex and MTL, and perhaps also between encoding during wake and reactivation during sleep (c.f., Gibson et al., 2022; Jiang et al., 2019a). In turn, weak encoding during wakefulness could result in sub-optimal coordination between the cortex and HC prior to a down-state, reducing precision in the reactivations selected for transfer to the cortex. In support of this, two recent studies showed distinct associations between low- and high-quality encoding with memory consolidation and measures of oscillatory activity (Denis et al., 2021; Muehlroth et al., 2020).

REM Sleep Theta Oscillations and Memory

The role of theta frequency activity, on its own and in synchrony with other sleep rhythms, is also relevant in the context of REM sleep-associated memory processes. The dominating focus on NREM sleep in this dissertation precludes discussion about the relative role of REM sleep and memory. A long line of evidence implicates the distinct (and complementary) neurophysiological and cellular mechanisms of REM sleep in memory consolidation (Aleisa, et al., 2011; Fishbein, 1971; Fishbein & Gutwein, 1977; Kim et al., 2005; Maquet et al., 2000; Purple et al., 2020; Schredl et al., 2001; Smith et al., 2004). Pre-sleep learning is associated with increased REM sleep duration and intensity (Schredl et al., 2001; Smith et al., 2004), and presence or amount of REM sleep is associated with retention of emotional stimuli (Wagner et al., 2001). As well, REM sleep deprivation can disrupt normal memory consolidation (Aleisa et al., 2011; Fishbein, 1971), possibly by inhibiting long-term potentiation in the HC (Kim et al., 2005). The memory-facilitating role of REM sleep may rely on acetylcholine and GABAergic neurotransmission (Boyce et al., 2016; Hornung et al., 2007; Schredl et al., 2001), and on calcium-mediated neuroplastic processes (Almeida-Filho et al., 2018). Of note, REM sleep duration declines with greater age (Floyd et al., 2007), as does REM theta (Scarpelli et al., 2019) and delta (Waterman et al., 1993) spectral power.

REM sleep theta activity has also been associated with memory consolidation in both animals and humans (see Puentes-Mestril et al., 2019 for review). In rats, REM sleep theta activity has been associated with the consolidation of cued fear-conditioning (Popa et al., 2010) and spatial memories (Zielinski et al., 2021). In humans, REM theta has been associated with emotional memory of a pre-sleep psychosocial stress (Kim et al., 2020), improvement in overnight declarative memory (Fogel et al., 2007), and recall of neutral (Lehmann et al., 2016) or negatively valenced emotional stimuli ($r = 0.61$; Nishida et al., 2009; see also Sopp et al., 2017). Greater REM theta also relates to more dream-references to pre-sleep waking experiences (Eichenlaub et al., 2018), and predicts successful dream recall (Marzano et al., 2011; Scarpelli et al., 2019). Coupling of theta phase (e.g., 4–7 Hz) and gamma (e.g., 20–100 Hz) power (theta-gamma coupling, or TGC) during REM has been observed in rodents (Alexander et al., 2018; Belluscio et al., 2012; Brankačk et al., 2012; Koike et al., 2017; Scheffzük et al., 2011; Tort et al., 2013); however, there is a paucity of studies examining REM TGC in humans (e.g., Abdullah & Cvetkovic, 2015; Cantero

et al., 2003), and especially in the context of ageing. One recent study of TGC during wake (Karlsson et al., 2022) showed that more precise TGC with the theta peak correlated with better associative memory performance, and that coupling phases were more varied in older versus younger adults.

Taken together, there is a considerable emphasis in the literature on examining coupling of NREM oscillations in the context of memory, which leaves a gap in knowledge about potential roles of coupled activity during REM sleep. Practically speaking, it may be harder to study coupled oscillations in REM sleep due to the difference in morphology and regularity of oscillations between NREM and REM stages, with NREM oscillations being easier to detect. Nevertheless, mounting evidence suggests that overnight memory processing is, in part, also facilitated by REM sleep, and by associated theta oscillation activity. This is consistent with proposals made by both the sequential and synaptic homeostasis hypotheses of sleep and memory (MacDonald & Cote, 2021; Giuditta, 2014; Tamaki et al., 2020), and is in-line with recent arguments to also consider the cyclic pattern of NREM and REM sleep across the night (Pereira & Lewish, 2020; Muehlroth, Rasch, & Werkle-Bergner, 2020; Strauss et al., 2022).

Practical and Clinical Implications

My two studies provide support for a guiding hypothesis that NREM SO-coupling with frontal slow spindle power may hold a functional significance in the context of ageing. Evidence from my studies adds to a growing understanding of potentially fundamental neural mechanisms of memory, and for how lifespan changes in coupled activity relates to age-related memory declines. Several authors have argued, and often in reference to the findings of Muehlroth et al. (2019), that slow spindle activity may not be involved in HC-dependent memory consolidation, and may instead be more related to cortico-cortical communication in-line with the SO. My two studies cannot infer about this one way or the other, but they provide an interesting balance to the discussion so-far that often mostly spotlights the role of coupling with fast spindle activity. In turn, perhaps my results will help inspire more rigorous examinations of memory-associated roles of CFC with slow spindle activity, and especially so in the context of ageing.

A more nuanced understanding of SO – σ CFC and its role in memory consolidation also helps to further the research efforts to examine the impact of non-pharmacological sleep-related interventions in

facilitating or boosting memory consolidation processes, such as transcranial electrical stimulation (Ladenbauer et al., 2017; Marshall et al., 2004; Marshall et al., 2006), auditory stimuli (Harrington et al., 2021; Krugliakova et al., 2020), and targeted memory reactivation (TMR; e.g., Cairney et al., 2014; Oudiette & Paller, 2013). See Barham and colleagues (2016) and Hu and colleagues (2020) for relevant meta-analyses. Increased knowledge about SO – σ CFC, in general and in the context of ageing, can help enhance the precision and fidelity of these sleep-related memory interventions, such as by accounting for ageing-related changes in brain activity to better "tune" the study intervention for older adults who may require specific settings or stimulus protocols relative to younger adults.

Results between younger and older adult groups also add support to the notion that declines in NREM CFC, and altered associations with memory, in healthy ageing may be pertinent for the study of cognitive decline in the context of abnormal ageing. With a growing ageing population comes a greater prevalence of dementia syndromes, such as mild cognitive impairment (MCI) and Alzheimer's disease (AD); accordingly, a recent study reported that the number of people living with dementia approximately doubles every five years, and there is a greater prevalence of AD in women than in men (Cao et al., 2020). There is evidence that AD-related pathology begins to develop many years before detectable symptoms are present, mainly in the forms of subjective cognitive decline and subsequent MCI (Leng et al., 2020; Petersen, 2004). Some have suggested that declines in NREM oscillations (e.g., SWA, spindles, SO – σ CFC) could be used to predict the burden or severity of dementia-related neuropathological markers, such as β-amyloid and tau, and there is some evidence to suggest this (Weng et al., 2020; Winer et al., 2019). While this thesis did not include data from cognitively impaired seniors, the altered phase-amplitude relations observed in my two older adult samples could suggest that similar, if not more dramatic, CFC changes may occur in the context of MCI or AD (e.g., Ladenbauer et al., 2021; Lloret et al., 2020). In turn, it is feasible to propose that measures of NREM CFC could act as a simple and non-invasive biomarker for the early detection, diagnosis, and longer-term monitoring of ageing-related neuro-degeneration; testing this hypothesis requires further study with healthy and clinical (MCI, AD) groups.

Limitations and Strengths

As indicated within each manuscript, there were important limitations and noteworthy strengths about each of my studies. The primary limitations of Study 1 included the availability of only an initial PSG screening night as the non-learning baseline, lack of control conditions, and a sample with mixed (absent to moderate) sleep apnea severity. Study 2 accounted for each of these Study 1 limitations, but had a smaller sample size, and the 40-item word-pair task may not have been challenging enough for the younger group. The main studies of YAs versus OAs that I have referred to throughout (Helfrich et al., 2018; Ladenbauer et al., 2021; Muehlroth et al., 2019, but not Schneider et al., 2020) each had a larger sample size (and in some cases with twice the number of OAs as in my Study 2). As a more general limitation of this thesis, both included studies were based on cross-sectional designs, which can only provide so much information about relations between brain (or other physiologic) activity and cognition, and both focused primarily on individual/univariate comparisons, whereas a multivariate approach (with a sufficient sample size) could provide a more nuanced picture of SO – σ CFC and relations with learning and memory across age groups. The question of age-related changes in CFC can be meaningfully addressed only through a prospective-longitudinal design with distant follow-up assessments.

Strengths of each study include having a sample of participants that were selected using stringent *a priori* inclusion criteria, a data-driven approach to measurement of CFC, and examining CFC and relations with memory across a range of analytical contexts and in consideration of pertinent data cleaning and pre-processing steps. As well, both studies leveraged their within-subjects design to examine associations with memory in the context of individual (relative) change in CFC between experimental conditions. The primary factor that allowed for this was that both studies showcased data from more than one recording visit, which many available studies of CFC and memory do not do (e.g., Bar et al., 2020; Göldi et al., 2019; Helfrich et al., 2018; Mikutta et al., 2019; Muehlroth et al., 2019). Lastly, analyses in this dissertation largely conformed to the CFC measurement guidelines suggested by Aru et al. (2015), and to the spirit and recommendations for EEG signal processing put forth by Cox and Fell (2020) and as applied to EEG sleep studies in the context of ageing by Muehlroth and Werkle-Bergner (2020).

Future Analysis Directions with the Present Data

The analyses in this dissertation allow for a starting point from which to explore more complex and nuanced analytical approaches. For instance, the results here about coupling strength are based on raw measures of MI (after log-transformation). Several studies (Cox et al., 2019 and 2020; Krugliakova et al., 2020; Malerba et al., 2018; Mikutta et al., 2019; Zhang et al., 2020) have employed a technique of deriving a normalized measure of MI, often obtained through z-scoring to a surrogate (null) distribution; this normalization is thought to help control extraneous noise, and allow one to test if the amount of coupling observed is significantly greater than chance (see Cox & Fell, 2020). The normalized MI, and accompanying significance test, can provide a meaningful descriptive tool to show how much coupling was actually observed. This metric, however, is not a direct measure of coupling strength, per se, and is more a reflection of difference (in SD-units) from an individualized surrogate distribution. Thus, future studies could systematically compare both raw and normalized MI measures to help inform the kinds of inferences that could be drawn about associations with memory and with ageing between the two metrics.

Results from both studies were also focused only on scalp-measured EEG data from the frontal midline (Fz) and from the cortical vertex (Cz) in the supplemental analyses. Data for my study were recorded using an 18-channel montage, allowing future studies to examine more complex coupling patterns across hemispheres and topographical regions, and across pairs or groups of distinct recording sites rather than within a single site (i.e., cross-channel CFC using cluster-based permutation analyses).

My focus on SO – σ CFC precluded an examination of coupling with other (faster) NREM oscillations. In turn, another future analysis would be to examine the role of CFC with gamma activity in memory and ageing, in both NREM and REM sleep. There is evidence that HC ripple activity is reflected elsewhere in the cortex in the form of gamma, that gamma oscillations have a similar coupling pattern with SOs (Le Van Quyen et al., 2010; Valderrama et al., 2012) and with spindles (Ayoub et al., 2012), and that gamma may also reflect encoding reactivations during sleep (Le Van Quyen et al., 2016; Mölle et al., 2004). Together, cortical gamma may reflect a down-stream "echo" of HC ripple activity (c.f., Le Van Quyen et al., 2010). However, it is an open question if patterns observed in cortical gamma frequencies can be similarly detected using scalp EEG, although there is some early evidence to suggest it can (Cox,

van Driel et al., 2014; Piantoni et al., 2013; Valderrama et al., 2012). Importantly, given valid concerns about signal contamination from high-frequency cranio-facial muscle artefacts (e.g., Goncharova et al., 2003; Hipp & Sigel, 2013; McMenamin et al., 2011; Pope et al., 2009; Whitham et al., 2007; see also Pfurtscheller & Cooper, 1975 and Yuval-Greenberg et al, 2008), analyses of gamma-coupling would need to account for this excess muscle activity with source-modelling techniques (e.g., Laplacian filtering) to maximize the signal-to-noise ratio (Babiloni et al., 2001; McFarland et al., 1997; Srinivasan et al., 1998).

Conclusions

This dissertation sought to address a question that, on the surface, was very simple: does this specific type of brain activity (coupled sleep oscillations) become altered with increasing age, and does it have a functional relationship with cognition (memory)? In the end, and as it was showcased throughout, the answer to this question may be an emphatic "it depends". Taken together, results from both studies offer new evidence for coupling dynamics between prominent NREM sleep oscillations in older age, and in relation to declarative memory performance. Whereas Study 1 suggested that SO – σ coupling phase distance closer to the up-state on the frontal channel in older adults predicted better memory consolidation, the same association was not found in Study 2 with an independent sample and an expanded protocol. However, Study 2 showcased age-group differences in coupling dynamics, and particularly with regards to coupling phase with slow spindle power on the frontal channel. Overall, this dissertation provides a thorough examination of SO – σ CFC in adults and in association with learning and declarative memory, and my findings highlight a potentially preserved relation between NREM CFC and overnight memory consolidation in older age. The most pertinent application of this kind of research is to examine SO – σ CFC in samples of older adults who are at-risk for ageing-related cognitive decline and AD, to elucidate if CFC measures could act as a reliable and non-invasive biomarker for dementia.

References

Abdullah, H., & Cvetkovic, D. (2015, May). Phase amplitude coupling of theta-gamma EEG frequency bands in sleep apnoea. *2015 International Conference on BioSignal Analysis, Processing and Systems (ICBAPS),* pp. 140-144. https://doi.org/10.1109/ICBAPS.2015.7292234

Achermann, P., & Borbely, A. A. (1997). Low-frequency (< 1Hz) oscillations in the human sleep electroencephalogram. *Neuroscience*, *81*(1), 213-222. https://doi.org/10.1016/s0306-4522(97)00186-3

Ackermann, S., & Rasch, B. (2014). Differential effects of non-REM and REM sleep on memory consolidation? *Current Neurology and Neuroscience Reports*, *14*(2), 430. https://doi.org/10.1007/s11910-013-0430-8

Akerstedt, T. (2006). Psychosocial stress and impaired sleep. *Scandinavian Journal of Work, Environment & Health*, *32*(6), 493–501. https://doi.org/10.5271/sjweh.1054

Aleisa, A. M., Alzoubi, K. H., & Alkadhi, K. A. (2011). Post-learning REM sleep deprivation impairs long-term memory: reversal by acute nicotine treatment. *Neuroscience Letters*, *499*(1), 28–31. https://doi.org/10.1016/j.neulet.2011.05.025

Alexander, A. S., Rangel, L. M., Tingley, D., & Nitz, D. A. (2018). Neurophysiological signatures of temporal coordination between retrosplenial cortex and the hippocampal formation. *Behavioral Neuroscience*, *132*(5), 453–468. https://doi.org/10.1037/bne0000254

Alger, S. E., Chambers, A. M., Cunningham, T., & Payne, J. D. (2015). The role of sleep in human declarative memory consolidation. *Current Topics in Behavioral Neurosciences*, *25*, 269–306. https://doi.org/10.1007/7854_2014_341

Almeida-Filho, D. G., Queiroz, C. M., & Ribeiro, S. (2018). Memory corticalization triggered by REM sleep: mechanisms of cellular and systems consolidation. *Cellular and Molecular Life Sciences: CMLS*, *75*(20), 3715–3740. https://doi.org/10.1007/s00018-018-2886-9

Ambrosini, M. V., & Giuditta, A. (2001). Learning and sleep: the sequential hypothesis. *Sleep Medicine Reviews*, *5*(6), 477–490. https://doi.org/10.1053/smrv.2001.0180

Amiri, M., Frauscher, B., & Gotman, J. (2016). Phase-amplitude coupling is elevated in deep sleep and in the onset zone of focal epileptic seizures. *Frontiers in Human Neuroscience*, *10*, 387. https://doi.org/10.3389/fnhum.2016.00387

Amzica, F. & Steriade, M. (1995). Disconnection of intracortical synaptic linkages disrupts synchronization of a slow oscillation. *The Journal of Neuroscience, 15*(6), 4658-4677. https://doi.org/10.1523/jneurosci.15-06-04658.1995

André, C., Tomadesso, C., de Flores, R., Branger, P., Rehel, S., Mézenge, F., Landeau, B., Sayette, V. de la, Eustache, F., Chételat, G., & Rauchs, G. (2019). Brain and cognitive correlates of sleep fragmentation in elderly subjects with and without cognitive deficits. *Alzheimer's & Dementia (Amsterdam, Netherlands)*, *11*(1), 142–150. https://doi.org/10.1016/j.dadm.2018.12.009

Aron, L., Zullo, J., & Yankner, B. A. (2022). The adaptive aging brain. *Current Opinion in Neurobiology*, *72*, 91–100. https://doi.org/10.1016/j.conb.2021.09.009

Aru, J., Aru, J., Priesemann, V., Wibral, M., Lana, L., Pipa, G., Singer, W., & Vicente, R. (2015). Untangling cross-frequency coupling in neuroscience. *Current Opinion in Neurobiology*, *31*, 51–61. https://doi.org/10.1016/j.conb.2014.08.002

Astori, S., Wimmer, R. D., & Lüthi, A. (2013). Manipulating sleep spindles – expanding views on sleep, memory, and disease. *Trends in Neuroscience*, *36*(12), 738–748. https://doi.org/10.1016/j.tins.2013.10.001

Axmacher, N., Elger, C. E., & Fell, J. (2008). Ripples in the medial temporal lobe are relevant for human memory consolidation. *Brain: A Journal of Neurology*, *131*(Pt 7), 1806–1817. https://doi.org/10.1093/brain/awn103

Ayoub, A., Mölle, M., Preissl, H., & Born, J. (2012). Grouping of MEG gamma oscillations by EEG sleep spindles. *NeuroImage*, *59*(2), 1491–1500. https://doi.org/10.1016/j.neuroimage.2011.08.023

Babiloni, F., Cincotti, F., Carducci, F., Rossini, P. M., & Babiloni, C. (2001). Spatial enhancement of EEG data by surface Laplacian estimation: the use of magnetic resonance imaging-based head

models. *Clinical Neurophysiology: Official Journal of the International Federation of Clinical Neurophysiology*, *112*(5), 724–727. https://doi.org/10.1016/s1388-2457(01)00494-1

Backhaus, J., Born, J., Hoeckesfeld, R., Fokuhl, S., Hohagen, F., & Junghanns, K. (2007). Midlife decline in declarative memory consolidation is correlated with a decline in slow wave sleep. *Learning & memory*, *14*(5), 336-341. https://doi.org/10.1101/lm.470507

Bandarabadi, M., Boyce, R., Gutierrez Herrera, C., Bassetti, C. L., Williams, S., Schindler, K., & Adamantidis, A. (2019). Dynamic modulation of theta-gamma coupling during rapid eye movement sleep. *Sleep*, *42*(12). https://doi.org/10.1093/sleep/zsz182

Bar, E., Marmelshtein, A., Arzi, A., Perl, O., Livne, E., Hizmi, E., Paz, R., Sobel, N., Dudai, Y., & Nir, Y. (2020). Local targeted memory reactivation in human sleep. *Current Biology*, *30*(8), 1435-1446.e5. https://doi.org/10.1016/j.cub.2020.01.091

Barham, M. P., Enticott, P. G., Conduit, R., & Lum, J. A. G. (2016). Transcranial electrical stimulation during sleep enhances declarative (but not procedural) memory consolidation: Evidence from a meta-analysis. *Neuroscience and Biobehavioral Reviews*, *63*, 65–77. https://doi.org/10.1016/j.neubiorev.2016.01.009

Bartsch, U., Simpkin, A. J., Demanuele, C., Wamsley, E., Marston, H. M., & Jones, M. W. (2019). Distributed slow-wave dynamics during sleep predict memory consolidation and its impairment in schizophrenia. *NPJ Schizophrenia*, ***5***(1), 1-11. https://doi.org/10.1038/s41537-019-0086-8

Bastian, L., Samanta, A., Ribeiro de Paula, D., Weber, F. D., Schoenfeld, R., Dresler, M., & Genzel, L. (2022). Spindle–slow oscillation coupling correlates with memory performance and connectivity changes in a hippocampal network after sleep. *Human Brain Mapping, 43*(13), 3923–3943. https://doi.org/10.1002/hbm.25893

Bastien, C. H., Vallières, A., & Morin, C. M. (2001). Validation of the Insomnia Severity Index as an outcome measure for insomnia research. *Sleep Medicine*, *2*(4), 297-307. https://doi.org/10.1016/s1389-9457(00)00065-4

Beck, A. T., Epstein, N., Brown, G., & Steer, R. (1993). Beck anxiety inventory. *Journal of Consulting and Clinical Psychology*. https://doi.org/10.1037/t02025-000

Beck, A. T., Steer, R. A., & Brown, G. (1996). Beck depression inventory–II. *Psychological Assessment*. https://doi.org/10.1037/t00742-000

Belluscio, M. A., Mizuseki, K., Schmidt, R., Kempter, R., & Buzsáki, G. (2012). Cross-frequency phase-phase coupling between theta and gamma oscillations in the hippocampus. *Journal of Neuroscience, 32*(2), 423-435. https://doi.org/10.1523/JNEUROSCI.4122-11.2012

Benedict, C., Byberg, L., Cedernaes, J., Hogenkamp, P. S., Giedratis, V., Kilander, L., Lind, L., Lannfelt, L., & Schiöth, H. B. (2015). Self-reported sleep disturbance is associated with Alzheimer's disease risk in men. *Alzheimer's & Dementia: The Journal of the Alzheimer's Association*, *11*(9), 1090–1097. https://doi.org/10.1016/j.jalz.2014.08.104

Berens, P. (2009). CircStat: a MATLAB toolbox for circular statistics. *Journal of Statistical Software*, *31*(1), 1-21. https://doi.org/10.18637/jss.v031.i10

Bersagliere, A., Pascual-Marqui, R. D., Tarokh, L., & Achermann, P. (2018). Mapping slow waves by EEG topography and source localization: effects of sleep deprivation. *Brain Topography*, *31*(2), 257-269. https://doi.org/10.1007/s10548-017-0595-6

Bjorness, T. E., Booth, V., & Poe, G. R. (2018). Hippocampal theta power pressure builds over non-REM sleep and dissipates within REM sleep episodes. *Archives Italiennes de Biologie*, *156*(3), 112–126. https://doi.org/10.12871/00039829201833

Blethyn, K. L., Huges, S. W., Tóth, T. I., Cope, D. W., & Crunelli, V. (2006). Neuronal basis of the slow (<1 Hz) oscillation in neurons of the nucleus reticularis thalami in vitro. *The Journal of Neuroscience, 26*(9), 2474-2486. https://doi.org/10.1523/JNEUROSCI.3607-05.2006

Bonanni, E., Di Coscio, E., Maestri, M., Carnicelli, L., Tsekou, H., Economou, N. T., Paparrigopoulos, T., Bonakis, A., Papageorgiou, S. G., Vassilopoulos, D., Soldatos, C. R., Murri, L., & Ktonas, P. Y. (2012). Differences in EEG delta frequency characteristics and patterns in slow-wave sleep between

dementia patients and controls: a pilot study: A pilot study. *Journal of Clinical Neurophysiology*, *29*(1), 50–54. https://doi.org/10.1097/WNP.0b013e318246b56d

Bódizs, R., Horváth, C. G., Szalárdy, O., Ujma, P. P., Simor, P., Gombos, F., Kovács, I., Genzel, L., & Dresler, M. (2022). Sleep-spindle frequency: Overnight dynamics, afternoon nap effects, and possible circadian modulation. *Journal of Sleep Research*, *31*(3), e13514. https://doi.org/10.1111/jsr.13514

Bódizs, R., Körmendi, J., Rigó, P., & Lázár, A. A. (2009). The individual adjustment method of sleep spindle analysis: Methodological improvements and roots in the fingerprint paradigm. *Journal of Neuroscience Methods, 178*(1), 205-213. http://doi.org/10.1016/j.jneumeth.2008.11.006

Borbély, A. A., & Achermann, P. (1999). Sleep homeostasis and models of sleep regulation. *Journal of Biological Rhythms*, *14*(6), 557–568. https://doi.org/10.1177/074873099129000894

Borbély, A. A., Tobler, I., & Hanagasioglu, M. (1984). Effect of sleep deprivation on sleep and EEG power spectra in the rat. *Behavioural Brain Research*, *14*(3), 171–182. https://doi.org/10.1016/0166-4328(84)90186-4

Boselli, M., Parrino, L., Smerieri, A., & Terzano, M. G. (1998). Effect of age on EEG arousals in normal sleep. *Sleep*, *21*(4), 351–357. https://doi.org/10.1093/sleep/21.4.361

Boyce, R., Glasgow, S. D., Williams, S., & Adamantidis, A. (2016). Causal evidence for the role of REM sleep theta rhythm in contextual memory consolidation. *Science*, 352(6287), 812–816. https://doi.org/10.1126/science.aad5252

Boynton, G., Vahabzadeh, A., Hammoud, S., Ruzicka, D. L., & Chervin, R. D. (2013). Validation of the STOP-BANG questionnaire among patients referred for suspected obstructive sleep apnea. *Journal of Sleep Disorders--Treatment & Care*, *2*(4), 1-20. https://doi.org/10.4172/2325-9639.1000121

Bradley, M. M., & Lang, P. J. (1999). *Affective norms for English words (ANEW): Instruction manual and affective ratings* (pp. 1-45). Technical report C-1, the center for research in psychophysiology, University of Florida.

Brankačk, J., Scheffzük, C., Kukushka, V. I., Vyssotski, A. L., Tort, A. B. L., & Draguhn, A. (2012). Distinct features of fast oscillations in phasic and tonic rapid eye movement sleep: Cross-frequency coupling in REM sleep. *Journal of Sleep Research*, *21*(6), 630–633. https://doi.org/10.1111/j.1365-2869.2012.01037.x

Bueno-Lopez, A., Eggert, T., Dorn, H., & Danker-Hopfe, H. (2019). Slow oscillatory transcranial direct current stimulation (so-tDCS) during slow wave sleep has no effects on declarative memory in healthy young subjects. *Brain Stimulation*, *12*(4), 948–958. https://doi.org/10.1016/j.brs.2019.02.012

Buysse, D. J., Monk, T. H., Carrier, J., & Begley, A. (2005). Circadian patterns of sleep, sleepiness, and performance in older and younger adults. *Sleep*, *28*(11), 1365–1376. https://doi.org/10.1093/sleep/28.11.1365

Buysse, D. J., Reynolds III, C. F., Monk, T. H., Hoch, C. C., Yeager, A. L., & Kupfer, D. J. (1991). Quantification of subjective sleep quality in healthy elderly men and women using the Pittsburgh Sleep Quality Index (PSQI). *Sleep*, *14*(4), 331-338. https://doi.org/10.1093/sleep/14.4.331

Buzsáki, G. (1996). The hippocampo-neocortical dialogue. *Cerebral Cortex (New York, N.Y.: 1991)*, *6*(2), 81–92. https://doi.org/10.1093/cercor/6.2.81

Buzsáki, G., & Draguhn, A. (2004). Neuronal oscillations in cortical networks. *Science*, *304*(5679), 1926-1929. https://doi.org/10.1126/science.1099745

Buzsáki, G. & de Silva, F. L. (2012). High frequency oscillations in the intact brain. *Progress in Neurobiology,* 98(3), 241-249. http://doi.org/10.1016/j.pneurobio.2012.02.004

Cairney, S. A., Ashton, J. E., Roshchupkina, A. A., & Sobczak, J. M. (2015). A dual role for sleep spindles in sleep-dependent memory consolidation? *The Journal of Neuroscience,* ***35***(36), 12328-12330. http://doi.org/10.1523/jneurosci.2463-15.2015

Cairney, S. A., Durrant, S. J., Hulleman, J., & Lewis, P. A. (2014). Targeted memory reactivation during slow wave sleep facilitates emotional memory consolidation. *Sleep*, *37*(4), 701–707, 707A. https://doi.org/10.5665/sleep.3572

Cairney, S. A., Guttesen, A. V., El Marj, N., & Staresina, B. P. (2018). Memory consolidation is linked to spindle-mediated information processing during sleep. *Current Biology*, *28*(6), 948-954. https://doi.org/10.1016/j.cub.2018.01.087

Canolty, R. T., & Knight, R. T. (2010). The functional role of cross-frequency coupling. *Trends in cognitive sciences*, *14*(11), 506-515. http://doi.org/10.1016/j.tics.2010.09.001

Cantero, J. L., Atienza, M., & Salas, R. M. (2000). Spectral features of EEG alpha activity in human REM sleep: two variants with different functional roles? *Sleep*, *23*(6), 746–750. https://doi.org/10.1093/sleep/23.6.1b

Cantero, J. L., Atienza, M., Stickgold, R., Kahana, M. J., Madsen, J. R., & Kocsis, B. (2003). Sleep-dependent θ oscillations in the human hippocampus and neocortex. *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience*, *23*(34), 10897–10903. https://doi.org/10.1523/jneurosci.23-34-10897.2003

Cao, Q., Tan, C.-C., Xu, W., Hu, H., Cao, X.-P., Dong, Q., Tan, L., & Yu, J.-T. (2020). The prevalence of dementia: A systematic review and meta-analysis. *Journal of Alzheimer's Disease: JAD*, *73*(3), 1157–1166. https://doi.org/10.3233/JAD-191092

Cappuccio, F. P., D'Elia, L., Strazzullo, P., & Miller, M. A. (2010). Sleep duration and all-cause mortality: a systematic review and meta-analysis of prospective studies. *Sleep*, *33*(5), 585–592. https://doi.org/10.1093/sleep/33.5.585

Carey, T. J., Moul, D. E., Pilkonis, P., Germain, A., & Buysse, D. J. (2005). Focusing on the experience of insomnia. *Behavioral Sleep Medicine*, *3*(2), 73–86. https://doi.org/10.1207/s15402010bsm0302_2

Carrier, J., Viens, I., Poirier, G., Robillard, R., Lafortune, M., Vandewalle, G., Martin, N., Barakat, M., Paquet, J., & Filipini, D. (2011). Sleep slow wave changes during the middle years of life. *The European Journal of Neuroscience*, *33*(4), 758–766. https://doi.org/10.1111/j.1460-9568.2010.07543.x

Clemens, Z., Fabó, D., & Halász, P. (2005). Overnight verbal memory retention correlates with the number of sleep spindles. *Neuroscience*, *132*, 529–535. https://doi.org/10.1016/j.neuroscience.2005.01.011

Clemens, Z., Fabó, D., & Halász, P. (2006). Twenty-four hours retention of visuospatial memory correlates with the number of parietal sleep spindles. *Neuroscience Letters*, *403*(1–2), 52–56. https://doi.org/10.1016/j.neulet.2006.04.035

Clemens, Z., Mölle, M., Erőss, L., Barsi, P., Halász, P., & Born, J. (2007). Temporal coupling of parahippocampal ripples, sleep spindles and slow oscillations in humans. *Brain*, *130*(11), 2868-2878. https://doi.org/10.1093/brain/awm146

Clemens, Z., Mölle, M., Erőss, L., Jakus, R., Rásonyi, G., Halász, P., & Born, J. (2011). Fine-tuned coupling between human parahippocampal ripples and sleep spindles. *The European Journal of Neuroscience*, *33*(3), 511-520. https://doi.org/10.1111/j.1460-9568.2010.07505.x

Clouter, A., Shapiro, K. L., & Hanslmayr, S. (2017). Theta phase synchronization is the glue that binds human associative memory. *Current Biology: CB*, *27*(20), 3143-3148.e6. https://doi.org/10.1016/j.cub.2017.09.001

Cole, S. R. & Voytek, B. (2017). Brain oscillations and the importance of waveform shape. *Trends in Cognitive Sciences, 21*(2), 137-149. http://doi.org/10.1016/j.tics.2016.12.008

Colgin, L. L. (2013). Mechanisms and functions of theta rhythms. *Annual Review of Neuroscience*, *36*(1), 295–312. https://doi.org/10.1146/annurev-neuro-062012-170330

Constant, I., & Sabourdin, N. (2012). The EEG signal: a window on the cortical brain activity: EEG in pediatric anesthesia. *Paediatric Anaesthesia*, *22*(6), 539–552. https://doi.org/10.1111/j.1460-9592.2012.03883.x

Contreras, D., & Steriade, M. (1995). Cellular basis of EEG slow rhythms: a study of dynamic corticothalamic relationships. *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience*, *15*(1), 604–622. https://doi.org/10.1523/jneurosci.15-01-00604.1995

Cordi, M. J., & Rasch, B. (2021). How robust are sleep-mediated memory benefits? *Current Opinion in Neurobiology*, *67*, 1–7. https://doi.org/10.1016/j.conb.2020.06.002

Corsi-Cabrera, M., Sifuentes-Ortega, R., Rosales-Lagarde, A., Rojas-Ramos, O. A., & Del Rio-Portilla, Y. (2014). Enhanced synchronization of gamma activity between frontal lobes during REM sleep as a function of REM sleep deprivation in man. *Experimental Brain Research, 232,* 1497-1508. http://doi.org/10.1007/s00221-013-3802-z

Cowan, E., Liu, A., Henin, S., Kothare, S., Devinsky, O., & Davachi, L. (2020). Sleep spindles promote the restructuring of memory representations in ventromedial prefrontal cortex through enhanced hippocampal-cortical functional connectivity. *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience*, *40*(9), 1909–1919. https://doi.org/10.1523/JNEUROSCI.1946-19.2020

Cox, R., van Driel, J., de Boer, M., & Talamini, L. M. (2014). Slow oscillations during sleep coordinate interregional communication in cortical networks. *The Journal of Neuroscience, 34*(50), 16890-16901. https://doi.org/10.1523/jneurosci.1953-14.2014

Cox, R., & Fell, J. (2020). Analyzing human sleep EEG: A methodological primer with code implementation. *Sleep Medicine Reviews*, *54*(101353), 101353. https://doi.org/10.1016/j.smrv.2020.101353

Cox, R., Hofman, W. F., de Boer, M., & Talamini, L. M. (2014). Local sleep spindle modulations in relation to specific memory cues. *NeuroImage*, *99*, 103–110. https://doi.org/10.1016/j.neuroimage.2014.05.028

Cox, R., Hofman, W. F., & Talamini, L. M. (2012). Involvement of spindles in memory consolidation is slow wave sleep-specific. *Learning & Memory, 19*(7), 264-267. https://doi.org/10.1101/lm.026252.112

Cox, R., Mylonas, D. S., Manoach, D. S., & Stickgold, R. (2018). Large-scale structure and individual fingerprints of locally coupled sleep oscillations. *Sleep*, *41*(12), zsy175. https://doi.org/10.1093/sleep/zsy175

Cox, R., Rüber, T., Staresina, B. P., & Fell, J. (2020). Phase-based coordination of hippocampal and neocortical oscillations during human sleep. *Communications Biology*, *3*(1), 176. https://doi.org/10.1038/s42003-020-0913-5

Cox, R., Schapiro, A. C., Manoach, D. S., & Stickgold, R. (2017). Individual differences in frequency and topography of slow and fast sleep spindles. *Frontiers in Human Neuroscience*, *11*, 433. https://doi.org/10.3389/fnhum.2017.00433

Creery, J. D., Oudiette, D., Antony, J. W., & Paller, K. A. (2015). Targeted memory reactivation during sleep depends on prior learning. *Sleep*, *38*(5), 755–763. https://doi.org/10.5665/sleep.4670

Cricco, M., Simonsick, E. M., & Foley, D. J. (2001). The impact of insomnia on cognitive functioning in older adults. *Journal of the American Geriatrics Society*, *49*(9), 1185–1189. https://doi.org/10.1046/j.1532-5415.2001.49235.x

Cross, N. E., Carrier, J., Postuma, R. B., Gosselin, N., Kakinami, L., Thompson, C., Chouchou, F., & Dang-Vu, T. T. (2019). Association between insomnia disorder and cognitive function in middle-aged and older adults: a cross-sectional analysis of the Canadian Longitudinal Study on Aging. *Sleep*, *42*(8). https://doi.org/10.1093/sleep/zsz114

Cross, Z. R., Helfrich, R. F., Corcoran, A. W., Kohler, M. J., Coussens, S., Zou-Williams, L., Schlesewsky, M., Gaskell, M. G., Knight, R. T., & Bornkessel-Schlesewsky, I. (2020). Spindle-slow oscillation coupling during sleep predicts sequence-based language learning. In *bioRxiv*. https://doi.org/10.1101/2020.02.13.948539

Cross, Z. R., Kohler, M. J., Schlesewsky, M., Gaskell, M. G., & Bornkessel-Schlesewsky, I. (2018). Sleep-dependent memory consolidation and incremental sentence comprehension: Computational dependencies during language learning as revealed by neuronal oscillations. *Frontiers in Human Neuroscience, 12*(18), 1-18. http://doi.org/10.3389/fnhum.2018.00018

Crowley, K., Trinder, J., Kim, Y., Carrington, M., & Colrain, I. M. (2002). The effects of normal aging on sleep spindle and K-complex production. *Clinical Neurophysiology*, *113*(10), 1615–1622. https://doi.org/10.1016/s1388-2457(02)00237-7

Crum, R. M., Anthony, J. C., Bassett, S. S., & Folstein, M. F. (1993). Population-based norms for the Mini-Mental State Examination by age and educational level. *JAMA: The Journal of the American Medical Association*, *269*(18), 2386-2391. https://doi.org/10.1001/jama.1993.03500180078038

Dang-Vu, T. T. (2012). Neuronal oscillations in sleep: Insights from functional neuroimaging. *Neuromolecular Medicine, 14,* 154-167. http://doi.org/10.1007/s12017-012-8166-1

Dang-Vu, T. T., Bonjean, M., Schabus, M., Boly, M., Darsaud, A., Desseilles, M., Degueldre, C., Balteau, E., Phillips, C., Luxen, A., Sejnowski, T. J., & Maquet, P. (2011). Interplay between spontaneous and induced brain activity during human non-rapid eye movement sleep. *PNAS*, *108*(37), 15438–15443. https://doi.org/10.1073/pnas.1112503108

Dang-Vu, T. T., McKinney, S. M., Buxton, O. M., Solet, J. M., & Ellenbogen, J. M. (2010). Spontaneous brain rhythms predict sleep stability in the face of noise. *Current Biology*, *20*(15), R626-R627. https://doi.org/10.1016/j.cub.2010.06.032

Dang-Vu, T. T., Schabus, M., Desseilles, M., Albouy, G., Boly, M., Darsaud, A., Gais, S., Rauchs, G., Sterpenich, V., Vandewalle, G., Carrier, J., Moonen, G., Balteau, E., Degueldre, C., Luxen, A., Phillips, C., & Maquet, P. (2008). Spontaneous neural activity during human slow wave sleep. *PNAS*, *105*(39), 15160–15165. https://doi.org/10.1073/pnas.0801819105

Davis, H., Davis, P. A., Loomis, A. L., Harvey, E. N., & Hobart, G. (1938). Human brain potentials during the onset of sleep. *Journal of Neurophysiology*, *1*(1), 24–38. https://doi.org/10.1152/jn.1938.1.1.24

De Gennaro, L., & Ferrara, M. (2003). Sleep spindles: an overview. *Sleep Medicine Reviews*, *7*(5), 423–440. https://doi.org/10.1053/smrv.2002.0252

De Gennaro, L., Ferrara, M., Vecchio, F., Curcio, G., & Bertini, M. (2005). An electroencephalographic fingerprint of human sleep. *Neuroimage, 26*(1), 114-122. https://doi.org/10.1016/j.neuroimage.2005.01.020

Deak, M. C., & Stickgold, R. (2010). Sleep and cognition. *Wiley Interdisciplinary Reviews: Cognitive Science*, *1*(4), 491-500. https://doi.org/10.1002/wcs.52

Deary, I. J., Corley, J., Gow, A. J., Harris, S. E., Houlihan, L. M., Marioni, R. E., Penke, L., Rafnsson, S. B., & Starr, J. M. (2009). Age-associated cognitive decline. *British Medical Bulletin*, *92*(1), 135–152. https://doi.org/10.1093/bmb/ldp033

Dehnavi, F., Koo-Poeggel, P. C., Ghorbani, M., & Marshall, L. (2021). Spontaneous slow oscillation—slow spindle features predict induced overnight memory retention. *Sleep*, *44*(10), zsab127. https://doi.org/10.1093/sleep/zsab127

Demanuele, C., Bartsch, U., Baran, B., Khan, S., Vangel, M. G., Cox, R., Hämäläinen, M., Jones, M. W., Stickgold, R., & Manoach, D. S. (2017). Coordination of slow waves with sleep spindles predicts sleep-dependent memory consolidation in schizophrenia. *Sleep*, *40*(1). https://doi.org/10.1093/sleep/zsw013

Denis, D., Kim, S. Y., Kark, S. M., Daley, R. T., Kensinger, E. A., & Payne, J. D. (2022). Slow oscillation-spindle coupling is negatively associated with emotional memory formation following stress. *The European Journal of Neuroscience*, *55*(9-10), 2632-2650. https://doi.org/10.1111/ejn.15132

Denis, D., Mylonas, D., Poskanzer, C., Bursal, V., Payne, J. D., & Stickgold, R. (2021). Sleep spindles preferentially consolidate weakly encoded memories. *Journal of Neuroscience*, *41*(18), 4088-4099. https://doi.org/10.1523/JNEUROSCI.0818-20.2021

Desseilles, M., Dang-Vu, T., Schabus, M., Sterpenich, V., Maquet, P., & Schwartz, S. (2008). Neuroimaging insights into the pathophysiology of sleep disorders. *Sleep*, *31*(6), 777–794. https://doi.org/10.1093/sleep/31.6.777

Dickey, C. W., Verzhbinsky, I. A., Jiang, X., Rosen, B. Q., Kajfez, S., Eskandar, E. N., Gonzalez-Martinez, J., Cash, S. C., & Halgren, E. (2021). Cortical ripples provide the conditions for consolidation during NREM sleep in humans. *bioRxiv, 10*(2021.05), 11-443637. https://doi.org/10.1101/2021.05.11.443637

Dijk, D. J., Beersma, D. G., & van den Hoofdakker, R. H. (1989). All night spectral analysis of EEG sleep in young adult and middle-aged male subjects. *Neurobiology of Aging*, *10*(6), 677–682. https://doi.org/10.1016/0197-4580(89)90004-3

Dijk, D.-J., & Lockley, S. W. (2002). Integration of human sleep-wake regulation and circadian rhythmicity. *Journal of Applied Physiology*, *92*(2), 852–862. https://doi.org/10.1152/japplphysiol.00924.2001

Dijk, D. J., Hayes, B., & Czeisler, C. A. (1993). Dynamics of electroencephalographic sleep spindles and slow wave activity in men: effect of sleep deprivation. *Brain Research*, *626*(1–2), 190–199. https://doi.org/10.1016/0006-8993(93)90579-c

Djonlagic, I., Mariani, S., Fitzpatrick, A. L., Van Der Klei, V. M. G. T. H., Johnson, D. A., Wood, A. C., Seeman, T., Nguyen, H. T., Prerau, M. J., Luchsinger, J. A., Dzierzewski, J. M., Rapp, S. R., Tranah, G. J., Yaffe, K., Burdick, K. E., Stone, K. L., Redline, S., & Purcell, S. M. (2021). Macro and micro sleep architecture and cognitive performance in older adults. *Nature Human Behaviour*, *5*(1), 123–145. https://doi.org/10.1038/s41562-020-00964-y

Dumay, N. (2016). Sleep not just protects memories against forgetting, it also makes them more accessible. *Cortex, 74*, 288-296. https://doi.org/10.1016/j.cortex.2015.06.007

Durmer, J. S., & Dinges, D. F. (2005). Neurocognitive consequences of sleep deprivation. *Seminars in Neurology*, *25*(1), 117–129. https://doi.org/10.1055/s-2005-867080

Dvorak, D., & Fenton, A. A. (2014). Toward a proper estimation of phase-amplitude coupling in neural oscillations. *Journal of Neuroscience Methods*, *225*, 42–56. https://doi.org/10.1016/j.jneumeth.2014.01.002

Edwards, B. A., O'Driscoll, D. M., Ali, A., Jordan, A. S., Trinder, J., & Malhotra, A. (2010). Aging and sleep: Physiology and pathophysiology, *Semin Respir Crit Care Med, 31*(5), 618-633. http://doi.org/10.1055/s-0030-1265902

Eggert, T., Dorn, H., Sauter, C., Nitsche, M. A., Bajbouj, M., & Danker-Hopfe, H. (2013). No effects of slow oscillatory transcranial direct current stimulation (tDCS) on sleep-dependent memory

consolidation in healthy elderly subjects. *Brain Stimulation*, *6*(6), 938–945. https://doi.org/10.1016/j.brs.2013.05.006

Eggert, T., Sauter, C., Dorn, H., Peter, A., Hansen, M.-L., Marasanov, A., & Danker-Hopfe, H. (2015). Individual stability of sleep spindle characteristics in healthy young males. *Schwerpunkt, 19,* 38-45. http://doi.org/10.1007/s1118-015-0694-x

Ego-Stengel, V., & Wilson, M. A. (2010). Disruption of ripple-associated hippocampal activity during rest impairs spatial learning in the rat. *Hippocampus*, *20*(1), 1–10. https://doi.org/10.1002/hipo.20707

Eichenlaub, J.-B., van Rijn, E., Gaskell, M. G., Lewis, P. A., Maby, E., Malinowski, J. E., Walker, M. P., Boy, F., & Blagrove, M. (2018). Incorporation of recent waking-life experiences in dreams correlates with frontal theta activity in REM sleep. *Social Cognitive and Affective Neuroscience*, *13*(6), 637–647. https://doi.org/10.1093/scan/nsy041

Eschenko, O., Ramadan, W., Mölle, M., Born, J., & Sara, S. J. (2008). Sustained increase in hippocampal sharp-wave ripple activity during slow-wave sleep after learning. *Learning & Memory*, *15*(4), 222–228. https://doi.org/10.1101/lm.726008

Esser, S. K., Hill, S. L., & Tononi, G. (2007). Sleep homeostasis and cortical synchronization: I. Modeling the effects of synaptic strength on sleep slow waves. *Sleep*, *30*(12), 1617–1630. https://doi.org/10.1093/sleep/30.12.1617

Feinberg, I., & Floyd, T. C. (1979). Systematic trends across the night in human sleep cycle. *Psychophysiology*, *16*(3), 283-291. https://doi.org/10.1111/j.1469-8986.1979.tb02991.x

Feld, G. B., Wilhelm, I., Ma, Y., Groch, S., Binkofski, F., Mölle, M., & Born, J. (2013). Slow wave sleep induced by GABA agonist tiagabine fails to benefit memory consolidation. *Sleep, 36*(9), 1317-1326. http://doi.org/10.5665/sleep.2954

Fell, J., Röschke, J., Mann, K., & Schäffner, C. (1996). Discrimination of sleep stages: a comparison between spectral and nonlinear EEG measures. *Electroencephalography and Clinical Neurophysiology*, *98*(5), 401-410. https://doi.org/10.1016/0013-4694(96)95636-9

Fernandez, L. M., & Lüthi, A. (2020). Sleep spindles: mechanisms and functions. *Physiological Reviews*, *100*(2), 805-868. https://doi.org/10.1152/physrev.00042.2018

Fernández-Ruiz, A., Oliva, A., Fermino de Oliveira, E., Rocha-Almeida, F., Tingley, D., & Buzsáki, G. (2019). Long-duration hippocampal sharp wave ripples improve memory. *Science*, *364*(6445), 1082–1086. https://doi.org/10.1126/science.aax0758

Fishbein, W. (1971). Disruptive effects of rapid eye movement sleep deprivation on long-term memory. *Physiology & Behavior*, *6*(4), 279–282. https://doi.org/10.1016/0031-9384(71)90155-7

Fishbein, W., & Gutwein, B. M. (1977). Paradoxical sleep and memory storage processes. *Behavioral Biology*, *19*(4), 425–464. https://doi.org/10.1016/s0091-6773(77)91903-4

Fisher, N.I. (1995). *Statistical Analysis of Circular Data*. Revised edition. Cambridge University Press.

Floyd, J. A., Janisse, J. J., Jenuwine, E. S., & Ager, J. W. (2007). Changes in REM-sleep percentage over the adult lifespan. *Sleep*, *30*(7), 829–836. https://doi.org/10.1093/sleep/30.7.829

Fogel, S., Martin, N., Lafortune, M., Barakat, M., Debas, K., Laventure, S., Latreille, V., Gagnon, J.-F., Doyon, J., & Carrier, J. (2012). NREM sleep oscillations and brain plasticity in aging. *Frontiers in Neurology*, *3*, 176. https://doi.org/10.3389/fneur.2012.00176

Fogel, S. M., Smith, C. T., & Cote, K. A. (2007). Dissociable learning-dependent changes in REM and non-REM sleep in declarative and procedural memory systems. *Behavioural Brain Research*, *180*(1), 48–61. https://doi.org/10.1016/j.bbr.2007.02.037

Fortier-Brochu, E., Beaulieu-Bonneau, S., Ivers, H., & Morin, C. M. (2012). Insomnia and daytime cognitive performance: a meta-analysis. *Sleep Medicine Reviews*, *16*(1), 83–94. https://doi.org/10.1016/j.smrv.2011.03.008

Fraga, F. J., Falk, T. H., Kanda, P. A. M., & Anghinah, R. (2013). Characterizing Alzheimer's disease severity via resting-awake EEG amplitude modulation analysis. *PloS One*, *8*(8), e72240. https://doi.org/10.1371/journal.pone.0072240

Freeman, D., Sheaves, B., Goodwin, G. M., Yu, L.-M., Nickless, A., Harrison, P. J., Emsley, R., Luik, A. I., Foster, R. G., Wadekar, V., Hinds, C., Gumley, A., Jones, R., Lightman, S., Jones, S., Bentall, R.,

Kinderman, P., Rowse, G., Brugha, T., … Espie, C. A. (2017). The effects of improving sleep on mental health (OASIS): a randomised controlled trial with mediation analysis. *The Lancet. Psychiatry*, *4*(10), 749–758. https://doi.org/10.1016/S2215-0366(17)30328-0

Gais, S., & Born, J. (2004). Low acetylcholine during slow-wave sleep is critical for declarative memory consolidation. *Proceedings of the National Academy of Sciences of the United States of America*, *101*(7), 2140–2144. https://doi.org/10.1073/pnas.0305404101

Gais, S., Mölle, M., Helms, K., & Born, J. (2002). Learning-dependent increases in sleep spindle density. *The Journal of Neuroscience*, *22*(15), 6830–6834. https://doi.org/20026697

Gaudreau, H., Carrier, J., & Montplaisir, J. (2001). Age-related modifications of NREM sleep EEG: from childhood to middle age. *Journal of Sleep Research*, *10*(3), 165–172. https://doi.org/10.1046/j.1365-2869.2001.00252.x

Genzel, L., Dresler, M., Wehrle, R., Grözinger, M., & Steiger, A. (2009). Slow wave sleep and REM sleep awakenings do not affect sleep dependent memory consolidation. *Sleep*, *32*(3), 302–310. https://doi.org/10.1093/sleep/32.3.302

Genzel, L., Kroes, M. C. W., Dresler, M., & Battaglia, F. P. (2014). Light sleep versus slow wave sleep in memory consolidation: a question of global versus local processes? *Trends in Neurosciences*, *37*(1), 10–19. https://doi.org/10.1016/j.tins.2013.10.002

Geva-Sagiv, M., & Nir, Y. (2019). Local sleep oscillations: Implications for memory consolidation. *Frontiers in Neuroscience*, *13*, 813. https://doi.org/10.3389/fnins.2019.00813

Gibson, T., Cross, Z. R., & Chatburn, A. (2022). Theta activity during encoding interacts with NREM sleep oscillations to predict memory generalization. *Frontiers in Human Neuroscience, 16*, 821191. https://doi.org/10.3389/fnhum.2022.821191

Girardeau, G., Benchenane, K., Wiener, S. I., Buzsáki, G., & Zugaro, M. B. (2009). Selective suppression of hippocampal ripples impairs spatial memory. *Nature Neuroscience*, *12*(10), 1222–1223. https://doi.org/10.1038/nn.2384

Girardeau, G., & Zugaro, M. (2011). Hippocampal ripples and memory consolidation. *Current Opinion in Neurobiology*, *21*(3), 452–459. https://doi.org/10.1016/j.conb.2011.02.005

Giuditta, A. (2014). Sleep memory processing: the sequential hypothesis. *Frontiers in Systems Neuroscience*, *8*, 219. https://doi.org/10.3389/fnsys.2014.00219

Giuditta, A., Ambrosini, M. V., Montagnese, P., Mandile, P., Cotugno, M., Zucconi, G. G., & Vescia, S. (1995). The sequential hypothesis of the function of sleep. *Behavioural Brain Research*, *69*(1–2), 157–166. https://doi.org/10.1016/0166-4328(95)00012-i

Goel, N., Rao, H., Durmer, J. S., & Dinges, D. F. (2009). Neurocognitive consequences of sleep deprivation. *Seminars in Neurology*, *29*(4), 320–339. https://doi.org/10.1055/s-0029-1237117

Göldi, M., van Poppel, E. A. M., Rasch, B., & Schreiner, T. (2019). Increased neuronal signatures of targeted memory reactivation during slow-wave up states. *Scientific Reports*, *9*(1), 2715. https://doi.org/10.1038/s41598-019-39178-2

Goncharova, I. I., McFarland, D. J., Vaughan, T. M., & Wolpaw, J. R. (2003). EMG contamination of EEG: Spectral and topographical characteristics. *Clinical Neurophysiology, 114*, 1580-1593. http://doi.org/10.1016/S1388-2457(03)00093-2

Gonzalez, C. E., Mak-McCully, R. A., Rosen, B. Q., Cash, S. S., Chauvel, P. Y., Bastuji, H., Rey, M., & Halgren, E. (2018). Theta bursts precede, and spindles follow, cortical and thalamic downstates in human NREM sleep. *The Journal of Neuroscience*, *38*(46), 9989–10001. https://doi.org/10.1523/JNEUROSCI.0476-18.2018

Gorgoni, M., Lauri, G., Truglia, H., Cordone, S., Sarasso, S., Scarpelli, S., Mangiaruga, A., D'Atri, A., Tempesta, D., Ferrara, M., Marra, C., Rossini, P. M., & De Gennaro, L. (2016). Parietal fast sleep spindle density decrease in Alzheimer disease and amnestic mild cognitive impairment. *Neural Plasticity,* 8376108. http://doi.org/10.1155/2016/8376108

Goutagny, R., Gu, N., Cavanagh, C., Jackson, J., Chabot, J.-G., Quirion, R., Krantic, S., & Williams, S. (2013). Alterations in hippocampal network oscillations and theta-gamma coupling arise before Aβ

overproduction in a mouse model of Alzheimer's disease. *The European Journal of Neuroscience*, *37*(12), 1896–1902. https://doi.org/10.1111/ejn.12233

Gruber, G., Anderer, P., Parapatics, S., Saletu, B., Schabus, M., Klimesch, W., Klösch, G., Sauter, C., & Zeitlhofer, J. (2015). Involvement of sleep spindles in overnight declarative memory stabilization: Effects of time of incidence and spindle type. *Somnologie, 19,* 30-37. http://doi.org/10.1007/s11818-015-0699-8

Gui, W.-J., Li, H.-J., Guo, Y.-H., Peng, P., Lei, X., & Yu, J. (2017). Age-related differences in sleep-based memory consolidation: A meta-analysis. *Neuropsychologia*, *97*, 46–55. https://doi.org/10.1016/j.neuropsychologia.2017.02.001

Hablitz, L. M., & Nedergaard, M. (2021). The glymphatic system. *Current Biology*, *31*(20), R1371–R1375. https://doi.org/10.1016/j.cub.2021.08.026

Hahn, M. A., Bothe, K., Heib, D., Schabus, M., Helfrich, R. F., & Hoedlmoser, K. (2022). Slow oscillation–spindle coupling strength predicts real-life gross-motor learning in adolescents and adults. *Elife*, *11*, e66761. https://doi.org/10.7554/eLife.66761

Hahn, M. A., Heib, D., Schabus, M., Hoedlmoser, K., & Helfrich, R. F. (2020). Slow oscillation-spindle coupling predicts enhanced memory formation from childhood to adolescence. *Elife*, *9*, e53730. https://doi.org/10.7554/eLife.53730

Hall, M., Baum, A., Buysse, D. J., Prigerson, H. G., Kupfer, D. J., & Reynolds, C. F. (1998). Sleep as a mediator of the stress-immune relationship. *Psychosomatic Medicine*, *60*(1), 48–51. https://doi.org/10.1097/00006842-199801000-00011

Haller, M., Donoghue, T., Peterson, E., Varma, P., Sebastian, P., Gao, R., Noto, T., Knight, R. T., Shestyuk, A., & Voytek, B. (2018). Parameterizing neural power spectra. In *bioRxiv*. https://doi.org/10.1101/299859

Hamm, V., Heraud, C., Cassel, J-C., Mathis, C., & Goutagny, R. (2015). Precocious alterations of brain oscillatory activity in Alzheimer's disease: A window of opportunity for early diagnosis and treatment. *Frontiers in Cellular Neuroscience, 9*(491), 1-6. http://doi.org/10.3389/fncel.2015.00491

Harrington, M. O., Ashton, J. E., Ngo, H.-V. V., & Cairney, S. A. (2021). Phase-locked auditory stimulation of theta oscillations during rapid eye movement sleep. *Sleep*, *44*(4). https://doi.org/10.1093/sleep/zsaa227

Hauglund, N. L., Pavan, C., & Nedergaard, M. (2020). Cleaning the sleeping brain – the potential restorative function of the glymphatic system. *Current Opinion in Physiology*, *15*, 1–6. https://doi.org/10.1016/j.cophys.2019.10.020

Helfrich, R. F., Lendner, J. D., Mander, B. A., Guillen, H., Paff, M., Mnatsakanyan, L., Vadera, S., Walker, M. P., Lin, J. J., & Knight, R. T. (2019). Bidirectional prefrontal-hippocampal dynamics organize information transfer during sleep in humans. *Nature Communications*, *10*(1), 3572. https://doi.org/10.1038/s41467-019-11444-x

Helfrich, R. F., Mander, B. A., Jagust, W. J., Knight, R. T., & Walker, M. P. (2018). Old brains come uncoupled in sleep: Slow wave-spindle synchrony, brain atrophy, and forgetting. *Neuron*, *97*(1), 221–230.e4. https://doi.org/10.1016/j.neuron.2017.11.020

van der Helm, E., Gujar, N., Nishida, M., & Walker, M. P. (2011). Sleep-dependent facilitation of episodic memory details. *PLoS ONE, 6*(11), e27421. http://doi.org/10.1371/journal.pone.0027421

Himanen, S.-L., Virkkala, J., Huhtala, H., & Hasan, J. (2002). Spindle frequencies in sleep EEG show U-shape within first four NREM sleep episodes. *Journal of Sleep Research*, *11*(1), 35–42. https://doi.org/10.1046/j.1365-2869.2002.00273.x

Hipp, J. F. & Siegel, M. (2013). Dissociating neuronal gamma-band activity from cranial and ocular muscle activity in EEG. *Frontiers in Human Neuroscience, 7*, 338. http://doi.org/10.3389/fnhum.2013.00338

Hoffman, K. L., Battaglia, F. P., Harris, K., MacLean, J. N., Marshall, L., & Mehta, M. R. (2007). The upshot of up states in the neocortex: From slow oscillations to memory formation. *The Journal of Neuroscience, 27*(44), 11838-11841. http://doi.org/10.1523/jneurosci.3501-07.2007

Holth, J. K., Patel, T. K., & Holtzman, D. M. (2017). Sleep in Alzheimer's disease–beyond amyloid. *Neurobiology of Sleep and Circadian Rhythms*, *2*, 4–14. https://doi.org/10.1016/j.nbscr.2016.08.002

Holz, J., Piosczyk, H., Feige, B., Spiegelhalder, K., Baglioni, C., Riemann, D., & Nissen, C. (2012). EEG sigma and slow-wave activity during NREM sleep correlate with overnight declarative and procedural memory consolidation. *Journal of Sleep Research*, *21*(6), 612-619. http://doi.org/10.1111/j.1365-2869.2012.01017.x

Horne, J. A., & Ostberg, O. (1976). A self-assessment questionnaire to determine morningness-eveningness in human circadian rhythms. *International Journal of Chronobiology*, *4*(2), 97–110.

Hornung, O. P., Regen, F., Danker-Hopfe, H., Schredl, M., & Heuser, I. (2007). The relationship between REM sleep and memory consolidation in old age and effects of cholinergic medication. *Biological Psychiatry*, *61*(6), 750–757. https://doi.org/10.1016/j.biopsych.2006.08.034

Hot, P., Rauchs, G., Bertran, F., Denise, P., Desgranges, B., Clochon, P., & Eustache, F. (2011). Changes in sleep theta rhythm are related to episodic memory impairment in early Alzheimer's disease. *Biological Psychology*, *87*(3), 334–339. https://doi.org/10.1016/j.biopsycho.2011.04.002

Hu, X., Cheng, L. Y., Chiu, M. H., & Paller, K. A. (2020). Promoting memory consolidation during sleep: A meta-analysis of targeted memory reactivation. *Psychological Bulletin*, *146*(3), 218–244. https://doi.org/10.1037/bul0000223

Hülsemann, M. J., Naumann, E., & Rasch, B. (2019). Quantification of phase-amplitude coupling in neuronal oscillations: comparison of phase-locking value, mean vector length, modulation index, and generalized-linear-modeling-cross-frequency-coupling. *Frontiers in Neuroscience*, *13*, 573. https://doi.org/10.3389/fnins.2019.00573

Hutchison, I. C., & Rathore, S. (2015). The role of REM sleep theta activity in emotional memory. *Frontiers in Psychology*, *6*, 1439. https://doi.org/10.3389/fpsyg.2015.01439

Hyafil, A. (2015). Misidentifications of specific forms of cross-frequency coupling: three warnings. *Frontiers in Neuroscience*, *9*, 370. https://doi.org/10.3389/fnins.2015.00370

Iber, C., Ancoli-Israel, S. Chesson Jr. A. L., & Quan, S. F. (2007). *The AASM manual for the scoring of sleep and associated events: Rules, terminology and technical specifications*. American Academy of Sleep Medicine: Westchester, IL.

Insel, P. S., Mohlenhoff, B. S., Neylan, T. C., Krystal, A. D., & Mackin, R. S. (2021). Association of sleep and β-amyloid pathology among older cognitively unimpaired adults. *JAMA Network Open*, *4*(7), e2117573. https://doi.org/10.1001/jamanetworkopen.2021.17573

Jensen, O., Spaak, E., & Park, H. (2016). Discriminating valid from spurious indices of phase-amplitude coupling. *ENeuro*, *3*(6). https://doi.org/10.1523/ENEURO.0334-16.2016

Jensen, O., Spaak, E., & Zumer, J. M. (2014). Human brain oscillations: From physiological mechanisms to analysis and cognition. In *Magnetoencephalography* (pp. 359–403). Springer Berlin Heidelberg.

Jiang, X., Gonzalez-Martinez, J., & Halgren, E. (2019a). Coordination of human hippocampal sharpwave ripples during NREM sleep with cortical theta bursts, spindles, downstates, and upstates. *The Journal of Neuroscience*, *39*(44), 8744–8761. https://doi.org/10.1523/JNEUROSCI.2857-18.2019

Jiang, X., Gonzalez-Martinez, J., & Halgren, E. (2019b). Posterior hippocampal spindle ripples co-occur with neocortical theta bursts and downstates-upstates, and phase-lock with parietal spindles during NREM sleep in humans. *The Journal of Neuroscience*, *39*(45), 8949–8968. https://doi.org/10.1523/JNEUROSCI.2858-18.2019

Jiang, X., Shamie, I., K. Doyle, W., Friedman, D., Dugan, P., Devinsky, O., Eskandar, E., Cash, S. S., Thesen, T., & Halgren, E. (2017). Replay of large-scale spatio-temporal patterns from waking during subsequent NREM sleep in human cortex. *Scientific Reports*, *7*(1). https://doi.org/10.1038/s41598-017-17469-w

Jin, K. (2010). Modern biological theories of aging. *Aging and Disease*, *1*(2), 72–74.

Johns, M. W. (1991). A new method for measuring daytime sleepiness: the Epworth sleepiness scale. S*leep*, *14*(6), 540-545. https://doi.org/10.1093/sleep/14.6.540

Johns, M. W. (1992). Reliability and factor analysis of the Epworth Sleepiness Scale. *Sleep*, *15*(4), 376-381. https://doi.org/10.1093/sleep/15.4.376

Ju, Y-E. S., McLeland, J. S., Toedebusch, C. D., Xiong, C., Fagan, A. M., Duntley, S. P., Morris, J. C., & Holtzman, D. M. (2013). Sleep quality and preclinical Alzheimer disease. *JAMA Neurology, 70*(5), 587-593. http://doi.org/10.1001/jamaneurol.2013.2334

Karlson, C. W., Gallagher, M. W., Olson, C. A., & Hamilton, N. A. (2013). Insomnia symptoms and well-being: Longitudinal follow-up. *Health Psychology*, *32*(3), 311–319. https://doi.org/10.1037/a0028186

Karlsson, A. E., Lindenberger, U., & Sander, M. C. (2022). Out of rhythm: Compromised precision of theta-gamma coupling impairs associative memory in old age. *The Journal of Neuroscience*, *42*(9), 1752–1764. https://doi.org/10.1523/JNEUROSCI.1678-21.2021

Keage, H. A. D., Banks, S., Yang, K. L., Morgan, K., Brayne, C., & Matthews, F. E. (2012). What sleep characteristics predict cognitive decline in the elderly? *Sleep Medicine*, *13*(7), 886–892. https://doi.org/10.1016/j.sleep.2012.02.003

Khodagholy, D., Gelinas, J. N., & Buzsáki, G. (2017). Learning-enhanced coupling between ripple oscillations in association cortices and hippocampus. *Science*, *358*(6361), 369–372. https://doi.org/10.1126/science.aan6203

Kim, J., Gulati, T., & Ganguly, K. (2019). Competing roles of slow oscillations and delta waves in memory consolidation versus forgetting. *Cell*, *179*(2), 514-526. https://doi.org/10.1016/j.cell.2019.08.040

Kim, E. Y., Mahmoud, G. S., & Grover, L. M. (2005). REM sleep deprivation inhibits LTP in vivo in area CA1 of rat hippocampus. *Neuroscience Letters*, *388*(3), 163–167. https://doi.org/10.1016/j.neulet.2005.06.057

Kim, S. Y., Kark, S. M., Daley, R. T., Alger, S. E., Rebouças, D., Kensinger, E. A., & Payne, J. D. (2020). Interactive effects of stress reactivity and rapid eye movement sleep theta activity on emotional memory formation. *Hippocampus*, *30*(8), 829–841. https://doi.org/10.1002/hipo.23138

Klinzing, J. G., Mölle, M., Weber, F., Supp, G., Hipp, J. F., Engel, A. K., & Born, J. (2016). Spindle activity phase-locked to sleep slow oscillations. *NeuroImage*, *134*, 607–616. https://doi.org/10.1016/j.neuroimage.2016.04.031

Klinzing, J. G., Niethard, N., & Born, J. (2019). Mechanisms of systems memory consolidation during sleep. *Nature Neuroscience*, *22*(10), 1598–1610. https://doi.org/10.1038/s41593-019-0467-3

Koike, B. D. V., Farias, K. S., Billwiller, F., Almeida-Filho, D., Libourel, P.-A., Tiran-Cappello, A., Parmentier, R., Blanco, W., Ribeiro, S., Luppi, P.-H., & Queiroz, C. M. (2017). Electrophysiological evidence that the retrosplenial cortex displays a strong and specific activation phased with hippocampal theta during paradoxical (REM) sleep. *The Journal of Neuroscience*, *37*(33), 8003–8013. https://doi.org/10.1523/JNEUROSCI.0026-17.2017

Kroeger, D., & Vetrivelan, R. (2023). To sleep or not to sleep - Effects on memory in normal aging and disease. *Aging Brain*, *3*(100068), 100068. https://doi.org/10.1016/j.nbas.2023.100068

Krugliakova, E., Volk, C., Jaramillo, V., Sousouri, G., & Huber, R. (2020). Changes in cross-frequency coupling following closed-loop auditory stimulation in non-rapid eye movement sleep. *Scientific Reports*, *10*(1), 10628. https://doi.org/10.1038/s41598-020-67392-w

Kumral, D., Matzerath, A., Leonhart, R., & Shönauer, M. (2022). Spindle-dependent memory consolidation in healthy adults: A meta-analysis. *BioRxiv,* 2022.07.18.500433. https://doi.org//10.1101/2022.07.18.500433

Kumral, D., Şansal, F., Cesnaite, E., Mahjoory, K., Al, E., Gaebler, M., Nikulin, V. V., & Villringer, A. (2020). BOLD and EEG signal variability at rest differently relate to aging in the human brain. *NeuroImage*, *207*(116373), 116373. https://doi.org/10.1016/j.neuroimage.2019.116373

Kurz, E.-M., Conzelmann, A., Barth, G. M., Renner, T. J., Zinke, K., & Born, J. (2021). How do children with autism spectrum disorder form gist memory during sleep? A study of slow oscillation-spindle coupling. *Sleep*, *44*(6). https://doi.org/10.1093/sleep/zsaa290

Ladenbauer, J., Ladenbauer, J., Külzow, N., de Boor, R., Avramova, E., Grittner, U., & Flöel, A. (2017). Promoting Sleep Oscillations and Their Functional Coupling by Transcranial Stimulation Enhances

Memory Consolidation in Mild Cognitive Impairment. *The Journal of Neuroscience, 37*(30), 7111–7124. https://doi.org/10.1523/JNEUROSCI.0260-17.2017

Ladenbauer, J., Ladenbauer, J., Külzow, N., & Flöel, A. (2021). Memory-relevant nap sleep physiology in healthy and pathological aging. *Sleep*, *44*(7), zsab002. https://doi.org/10.1093/sleep/zsab002

Lafortune, M., Gagnon, J.-F., Martin, N., Latreille, V., Dubé, J., Bouchard, M., Bastien, C., & Carrier, J. (2014). Sleep spindles and rapid eye movement sleep as predictors of next morning cognitive performance in healthy middle-aged and older participants. *Journal of Sleep Research*, *23*(2), 159–167. https://doi.org/10.1111/jsr.12108

Latchoumane, C. F. V., Ngo, H. V. V., Born, J., & Shin, H. S. (2017). Thalamic spindles promote memory formation during sleep through triple phase-locking of cortical, thalamic, and hippocampal rhythms. *Neuron*, *95*(2), 424-435. https://doi.org/10.1016/j.neuron.2017.06.025

Laufs, H. (2008). Endogenous brain oscillations and related networks detected by surface EEG-combined fMRI. *Human Brain Mapping*, *29*(7), 762–769. https://doi.org/10.1002/hbm.20600

Le Van Quyen, M., Muller, L. E., 2nd, Telenczuk, B., Halgren, E., Cash, S., Hatsopoulos, N. G., Dehghani, N., & Destexhe, A. (2016). High-frequency oscillations in human and monkey neocortex during the wake-sleep cycle. *Proceedings of the National Academy of Sciences of the United States of America*, *113*(33), 9363–9368. https://doi.org/10.1073/pnas.1523583113

Le Van Quyen, M., Staba, R., Bragin, A., Dickson, C., Valderrama, M., Fried, I., & Engel, J. (2010). Large-scale microelectrode recordings of high-frequency gamma oscillations in human cortex during sleep. *The Journal of Neuroscience*, *30*(23), 7770–7782. https://doi.org/10.1523/JNEUROSCI.5049-09.2010

Lehmann, M., Schreiner, T., Seifritz, E., & Rasch, B. (2016). Emotional arousal modulates oscillatory correlates of targeted memory reactivation during NREM, but not REM sleep. *Scientific Reports*, *6*(1). https://doi.org/10.1038/srep39229

Lemola, S., & Richter, D. (2012). The course of subjective sleep quality in middle and old adulthood and its relation to physical health. *SSRN Electronic Journal*. https://doi.org/10.2139/ssrn.2182559

Leng, M., Yin, H., Zhang, P., Jia, Y., Hu, M., Li, G., Wang, C., & Chen, L. (2020). Sleep quality and health-related quality of life in older people with subjective cognitive decline, mild cognitive impairment, and Alzheimer disease. *The Journal of Nervous and Mental Disease*, *208*(5), 387–396. https://doi.org/10.1097/NMD.0000000000001137

Leung, L.-W. S. (1984). Theta rhythm during REM sleep and waking: Correlations between power, phase and frequency. *Electroencephalography and Clinical Neurophysiology*, *58*(6), 553–564. https://doi.org/10.1016/0013-4694(84)90045-2

Li, D., Ni, M., & Dun, S. (2015). Phase-amplitude coupling in human scalp EEG during NREM sleep. In *Biomedical Engineering and Informatics (BMEI), 2015 8th International Conference* (pp. 219-223). IEEE.

Lichstein, K. L., Durrence, H. H., Riedel, B., Taylor, D. J., & Bush, A. J. (2004). A review of epidemiological studies of insomnia and sleep. *Epidemiology of Sleep: Age, Gender and Ethnicity. Mahwah, NJ: Lawrence Erlbaum Associates, Inc*, 9-41.

Lim, A. S. P., Yu, L., Kowgier, M., Schneider, J. A., Buchman, A. S., & Bennett, D. A. (2013). Modification of the relationship of the apolipoprotein E e4 allele to the risk of Alzheimer disease and neurofibrillary tangle density by sleep. *JAMA Neurology, 70*(12), 1544-1551. http://doi.org/10.1001/jamaneurol.2013.4125

Lin, C.-L., Lin, C.-P., & Sun, J.-C. (2022). Experiences of middle-aged and older Taiwanese adults with chronic insomnia: A descriptive qualitative study. *Journal of Gerontological Nursing*, *48*(11), 21–28. https://doi.org/10.3928/00989134-20221003-06

Lloret, M.-A., Cervera-Ferri, A., Nepomuceno, M., Monllor, P., Esteve, D., & Lloret, A. (2020). Is sleep disruption a cause or consequence of Alzheimer's disease? Reviewing its possible role as a biomarker. *International Journal of Molecular Sciences*, *21*(3), 1168. https://doi.org/10.3390/ijms21031168

Lucey, B. P. & Bateman, R. J. (2014). Amyloid- β diurnal pattern: Possible role of sleep in Alzheimer's disease pathogenesis. *Neurobiology of Aging*, 35, S29-S34. http://doi.org/10.1016/j.neurobiolaging.2014.03.035

Lucey, B. P., Wisch, J., Boerwinkle, A. H., Landsness, E. C., Toedebusch, C. D., McLeland, J. S., Butt, O. H., Hassenstab, J., Morris, J. C., Ances, B. M., & Holtzman, D. M. (2021). Sleep and longitudinal cognitive performance in preclinical and early symptomatic Alzheimer's disease. *Brain*, *144*(9), 2852–2862. https://doi.org/10.1093/brain/awab272

Lüthi, A. (2014). Sleep spindles: Where they come from, what they do: Where they come from, what they do. *The Neuroscientist*, *20*(3), 243–256. https://doi.org/10.1177/1073858413500854

Luppi, P-H., Clement, O., Sapin, E., Peyron, C., Gervasoni, D., Leger, L., & Fort, P. (2012). Brainstem mechanisms of paradoxical (REM) sleep generation. *European Journal of Physiology, 463,* 43-52. http://doi.org/10.1007/s00424-011-1054-y

Magni, E., Binetti, G., Bianchetti, A., Rozzini, R., & Trabucchi, M. (1996). Mini-Mental State Examination: a normative study in Italian elderly population. *European Journal of Neurology*, *3*(3), 198-202. https://doi.org/10.1111/j.1468-1331.1996.tb00423.x

Mak-McCully, R. A., Rolland, M., Sargsyan, A., Gonzalez, C., Magnin, M., Chauvel, P., Rey, M., Bastuji, H., & Halgren, E. (2017). Coordination of cortical and thalamic activity during non-REM sleep in humans. *Nature Communications*, *8*(1), 15499. https://doi.org/10.1038/ncomms15499

Malerba, P., Whitehurst, L. N., Simons, S. B., & Mednick, S. C. (2018). Spatio-temporal structure of sleep slow oscillations on the electrode manifold and its relation to spindles. *Sleep*, *42*(1), 1–14. https://doi.org/10.1093/sleep/zsy197

Mander, B. A., Marks, S. M., Vogel, J. W., Rao, V., Lu, B., Saletin, J. M., Ancoli-Israel, S., Jagust, W. J., & Walker, M. P. (2015). β-amyloid disrupts human NREM slow waves and related hippocampus-dependent memory consolidation. *Nature Neuroscience*, *18*(7), 1051–1057. https://doi.org/10.1038/nn.4035

Mander, B. A., Rao, V., Lu, B., Saletin, J. M., Ancoli-Israel, S., Jagust, W. J., & Walker, M. P. (2014). Impaired prefrontal sleep spindle regulation of hippocampal-dependent learning in older adults. *Cerebral Cortex*, *24*(12), 3301–3309. https://doi.org/10.1093/cercor/bht188

Mander, B. A., Rao, V., Lu, B., Saletin, J. M., Lindquist, J. R., Ancoli-Israel, S., Jagust, W., & Walker, M. P. (2013). Prefrontal atrophy, disrupted NREM slow waves and impaired hippocampal-dependent memory in aging. *Nature Neuroscience*, *16*(3), 357–364. https://doi.org/10.1038/nn.3324

Maquet, P., Laureys, S., Peigneux, P., Fuchs, S., Petiau, C., Phillips, C., Aerts, J., Del Fiore, G., Degueldre, C., Meulemans, T., Luxen, A., Franck, G., Van Der Linden, M., Smith, C., & Cleeremans, A. (2000). Experience-dependent changes in cerebral activation during human REM sleep. *Nature Neuroscience*, *3*(8), 831–836. https://doi.org/10.1038/77744

Marshall, L., Helgadóttir, H., Mölle, M., & Born, J. (2006). Boosting slow oscillations during sleep potentiates memory. *Nature*, *444*(7119), 610–613. https://doi.org/10.1038/nature05278

Marshall, L., Mölle, M., Hallschmid, M., & Born, J. (2004). Transcranial direct current stimulation during sleep improves declarative memory. *The Journal of Neuroscience*, *24*(44), 9985–9992. https://doi.org/10.1523/JNEUROSCI.2725-04.2004

Martin, N., Lafortune, M., Godbout, J., Barakat, M., Robillard, R., Poirier, G., …, & Carrier, J. (2013). Topography of age-related changes in sleep spindles. *Neurobiology of Aging, 34*(2), 468-476. https://doi.org/10.1016/j.neurobiolaging.2012.05.020

Marzano, C., Ferrara, M., Mauro, F., Moroni, F., Gorgoni, M., Tempesta, D., Cipolli, C., & De Gennaro, L. (2011). Recalling and forgetting dreams: theta and alpha oscillations during sleep predict subsequent dream recall. *The Journal of Neuroscience*, *31*(18), 6674–6683. https://doi.org/10.1523/JNEUROSCI.0412-11.2011

Massimini, M., Huber, R., Ferrarelli, F., Hill, S., & Tononi, G. (2004). The sleep slow oscillation as a traveling wave. *The Journal of Neuroscience, 24*(31), 6862-6870. https://doi.org/10.1523/jneurosci.1318-04.204

Mayer, G., Jennum, P., Riemann, D., & Dauvilliers, Y. (2011). Insomnia in central neurologic diseases–occurrence and management. *Sleep Medicine Reviews*, *15*(6), 369-378. https://doi.org/10.1016/j.smrv.2011.01.005

McConnell, B. V., Kronberg, E., Medenblik, L. M., Kheyfets, V. O., Ramos, A. R., Sillau, S. H., Pulver, R. L., & Bettcher, B. M. (2022). The rise and fall of slow wave tides: Vacillations in coupled slow wave/spindle pairing shift the composition of slow wave activity in accordance with depth of sleep. *Frontiers in Neuroscience*, *16*, 915934. https://doi.org/10.3389/fnins.2022.915934

MacDonald, K. J., & Cote, K. A. (2021). Contributions of post-learning REM and NREM sleep to memory retrieval. *Sleep Medicine Reviews*, *59*, 101453. https://doi.org/10.1016/j.smrv.2021.101453

McFarland, D. J., McCane, L. M., David, S. V., & Wolpaw, J. R. (1997). Spatial filter selection for EEG-based communication. *Electroencephalography and Clinical Neurophysiology*, *103*(3), 386–394. https://doi.org/10.1016/s0013-4694(97)00022-2

McKenna, J. T., Zielinski, M. R., & McCarley, R. W. (2017). Neurobiology of REM sleep, NREM sleep homeostasis, and gamma band oscillations. In *Sleep Disorders Medicine* (pp. 55-77). Springer, New York, NY.

McMenamin, B. W., Shackman, A. J., Greischar, L. L., & Davidson, R. J. (2011). Electromyogenic artifacts and electroencephalographic inferences revisited. *NeuroImage*, *54*(1), 4–9. https://doi.org/10.1016/j.neuroimage.2010.07.057

Medic, G., Wille, M., & Hemels, M. E. (2017). Short- and long-term health consequences of sleep disruption. *Nature and Science of Sleep*, *9*, 151–161. https://doi.org/10.2147/NSS.S134864

Menicucci, D., Piarulli, A., Debarnot, U., d'Ascanio, P., Landi, A., & Gemignani, A. (2009). Functional structure of spontaneous sleep slow oscillation activity in humans. *PloS One*, *4*(10), e7601. https://doi.org/10.1371/journal.pone.0007601

Meyers, L. S., Gamst, G., & Guarino, A. J. (2013). *Applied Multivariate Research: Design and Interpretation* (2nd ed.). Sage Publications: Los Angeles.

Mikutta, C., Feige, B., Maier, J. G., Hertenstein, E., Holz, J., Riemann, D., & Nissen, C. (2019). Phase-amplitude coupling of sleep slow oscillatory and spindle activity correlates with overnight memory consolidation. *Journal of Sleep Research*. *28*(6), e12835. https://doi.org/10.1111/jsr.12835

Mitteldorf, J. (2010). Aging is not a process of wear and tear. *Rejuvenation Research*, *13*(2–3), 322–326. https://doi.org/10.1089/rej.2009.0967

Mölle, M., Bergmann, T. O., Marshall, L., & Born, J. (2011). Fast and slow spindles during the sleep slow oscillation: Disparate coalescence and engagement in memory processing. *Sleep*, *34*(10), 1411-1421. https://doi.org/10.5665/SLEEP.1290

Mölle, M., & Born, J. (2009). Hippocampus whispering in deep sleep to prefrontal cortex—for good memories? *Neuron*, *61*(4), 496-498. https://doi.org/10.1016/j.neuron.2009.02.002

Mölle, M., Eschenko, O., Gais, S., Sara, S. J., & Born, J. (2009). The influence of learning on sleep slow oscillations and associated spindles and ripples in humans and rats. *European Journal of Neuroscience*, *29*(5), 1071-1081. https://doi.org/10.1111/j.1460-9568.2009.06654.x

Mölle, M., Marshall, L., Gais, S., & Born, J. (2002). Grouping of spindle activity during slow oscillations in human non-rapid eye movement sleep. *The Journal of Neuroscience*, *22*(24), 10941-10947. https://doi.org/10.1523/jneurosci.22-24-10941.2002

Mölle, M., Marshall, L., Gais, S., & Born, J. (2004). Learning increases human electroencephalographic coherence during subsequent slow sleep oscillations. *PNAS*, *101*(38), 13963-13968. https://doi.org/10.1073/pnas.0402820101

Mölle, M., Yeshenko, O., Marshall, L., Sara, S. J., & Born, J. (2006). Hippocampal sharp wave-ripples linked to slow oscillations in rat slow-wave sleep. *Journal of Neurophysiology*, *96*(1), 62–70. https://doi.org/10.1152/jn.00014.2006

Montgomery, S. M., Sirota, A., & Buzsáki, G. (2008). Theta and gamma coordination of hippocampal networks during waking and rapid eye movement sleep. *The Journal of Neuroscience*, *28*(26), 6731–6741. https://doi.org/10.1523/JNEUROSCI.1227-08.2008

Moraes, W., Piovezan, R., Poyares, D., Bittencourt, L. R., Santos-Silva, R., & Tufik, S. (2014). Effects of aging on sleep structure throughout adulthood: a population-based study. *Sleep Medicine*, *15*(4), 401–409. https://doi.org/10.1016/j.sleep.2013.11.791

Morin, C. M., Belleville, G., Bélanger, L., & Ivers, H. (2011). The Insomnia Severity Index: psychometric indicators to detect insomnia cases and evaluate treatment response. *Sleep*, *34*(5), 601-608. https://doi.org/10.1093/sleep/34.5.601

Morin, A., Doyon, J., Dostie, V., Barakat, M., Hadj Tahar, A., Korman, M., Benali, H., Karni, A., Ungerleider, L. G., & Carrier, J. (2008). Motor sequence learning increases sleep spindles and fast frequencies in post-training sleep. *Sleep*, *31*(8), 1149–1156. https://doi.org/10.5665/sleep/31.8.1149

Morin, C. M., LeBlanc, M., Daley, M., Gregoire, J. P., & Mérette, C. (2006). Epidemiology of insomnia: prevalence, self-help treatments, consultations, and determinants of help-seeking behaviors. *Sleep Medicine*, *7*(2), 123–130. https://doi.org/10.1016/j.sleep.2005.08.008

Morrell, M. J., Finn, L., McMillan, A., & Peppard, P. E. (2012). The impact of ageing and sex on the association between sleepiness and sleep disordered breathing. *The European Respiratory Journal*, *40*(2), 386–393. https://doi.org/10.1183/09031936.00177411

Morris, J. C., Storandt, M., Miller, J. P., McKeel, D. W., Price, J. L., Rubin, E. H., & Berg, L. (2001). Mild cognitive impairment represents early-stage Alzheimer disease. *Archives of Neurology*, *58*(3), 397–405. https://doi.org/10.1001/archneur.58.3.397

Muehlroth, B. E., Rasch, B., & Werkle-Bergner, M. (2020). Episodic memory consolidation during sleep in healthy aging. *Sleep Medicine Reviews*, *52*, 101304. https://doi.org/10.1016/j.smrv.2020.101304

Muehlroth, B. E., Sander, M. C., Fandakova, Y., Grandy, T. H., Rasch, B., Shing, Y. L., & Werkle-Bergner, M. (2019). Precise slow oscillation–spindle coupling promotes memory consolidation in younger and older adults. *Scientific Reports*, *9*(1), 1940. https://doi.org/10.1038/s41598-018-36557-z

Muehlroth, B. E., Sander, M. C., Fandakova, Y., Grandy, T. H., Rasch, B., Shing, Y. L., & Werkle-Bergner, M. (2020). Memory quality modulates the effect of aging on memory consolidation during

sleep: Reduced maintenance but intact gain. *NeuroImage*, *209*, 116490. https://doi.org/10.1016/j.neuroimage.2019.116490

Muehlroth, B. E., & Werkle-Bergner, M. (2020). Understanding the interplay of sleep and aging: Methodological challenges. *Psychophysiology*, *57*(3), e13523. https://doi.org/10.1111/psyp.13523

Munch, M., Knoblauch, V., Blatter, K., Schroder, C., Schnitzler, C., Krauchi, K., Wirz-Justice, A., & Cajochen, C. (2004). The frontal predominance in human EEG delta activity after sleep loss decreases with age. *European Journal of Neuroscience, 20*, 1402-1410. http://doi.org/10.1111/j.1460-9568.2004.03580.x

Mylonas, D., Baran, B., Demanuele, C., Cox, R., Vuper, T. C., Seicol, B. J., Fowler, R. A., Correll, D., Parr, E., Callahan, C. E., Morgan, A., Henderson, D., Vangel, M., Stickgold, R., & Manoach, D. S. (2020). The effects of eszopiclone on sleep spindles and memory consolidation in schizophrenia: a randomized clinical trial. *Neuropsychopharmacology*, *45*(13), 2189–2197. https://doi.org/10.1038/s41386-020-00833-2

Mylonas, D., Machado, S., Larson, O., Patel, R., Cox, R., Vangel, M., Maski, K., Stickgold, R., & Manoach, D. S. (2022). Dyscoordination of non-rapid eye movement sleep oscillations in autism spectrum disorder. *Sleep*, *45*(3). https://doi.org/10.1093/sleep/zsac010

Nasreddine, Z. S., Phillips, N. A., Bédirian, V., Charbonneau, S., Whitehead, V., Collin, I., Cummings, J. L., & Chertkow, H. (2005). The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. *Journal of the American Geriatrics Society*, *53*(4), 695–699. https://doi.org/10.1111/j.1532-5415.2005.53221.x

Nedergaard, M., & Goldman, S. A. (2020). Glymphatic failure as a final common pathway to dementia. *Science (New York, N.Y.)*, *370*(6512), 50–56. https://doi.org/10.1126/science.abb8739

Ngo, H. V., Fell, J., & Staresina, B. (2020). Sleep spindles mediate hippocampal-neocortical coupling during long-duration ripples. E*life*, *9*, e57011. https://doi.org/10.7554/eLife.57011

Ngo, H. V. V., Martinetz, T., Born, J., & Mölle, M. (2013). Auditory closed-loop stimulation of the sleep slow oscillation enhances memory. *Neuron*, *78*(3), 545-553. https://doi.org/10.1016/j.neuron.2013.03.006

Niknazar, M., Krishnan, G. P., Bazhenov, M., & Mednick, S. C. (2015). Coupling of thalamocortical sleep oscillations are important for memory consolidation in humans. *PloS One*, *10*(12), e0144720. https://doi.org/10.1371/journal.pone.0144720

Nishida, M., Hirai, N., Miwakeichi, F., Maehara, T., Kawai, K., Shimizu, H., & Uchida, S. (2004). Theta oscillation in the human anterior cingulate cortex during all-night sleep: an electrocorticographic study. *Neuroscience Research*, *50*(3), 331–341. https://doi.org/10.1016/j.neures.2004.08.004

Nishida, M., Pearsall, J., Buckner, R. L., & Walker, M. P. (2009). REM sleep, prefrontal theta, and the consolidation of human emotional memory. *Cerebral Cortex*, *19*(5), 1158–1166. https://doi.org/10.1093/cercor/bhn155

Nuñez, A., & Buño, W. (2021). The theta rhythm of the hippocampus: From neuronal and circuit mechanisms to behavior. *Frontiers in Cellular Neuroscience, 15*, 649262. https://doi.org/10.3389/fncel.2021.649262

O'Byrne, J. N., Berman Rosa, M., Gouin, J.-P., & Dang-Vu, T. T. (2014). Neuroimaging findings in primary insomnia. *Pathologie-Biologie*, *62*(5), 262–269. https://doi.org/10.1016/j.patbio.2014.05.013

Ohayon, M. M., Carskadon, M. A., Guilleminault, C., & Vitiello, M. V. (2004). Meta-analysis of quantitative sleep parameters from childhood to old age in healthy individuals: developing normative sleep values across the human lifespan. *Sleep*, *27*(7), 1255–1273. https://doi.org/10.1093/sleep/27.7.1255

Ohayon, M. M., & Vecchierini, M.-F. (2005). Normative sleep data, cognitive function and daily living activities in older adults in the community. *Sleep*, *28*(8), 981–989. https://doi.org/10.1093/sleep/28.8.981

Ohki, T. (2022). Measuring phase-amplitude coupling between neural oscillations of different frequencies via the Wasserstein distance. *Journal of Neuroscience Methods*, *374*(109578), 109578. https://doi.org/10.1016/j.jneumeth.2022.109578

Olaithe, M., Bucks, R. S., Hillman, D. R., & Eastwood, P. R. (2018). Cognitive deficits in obstructive sleep apnea: Insights from a meta-review and comparison with deficits observed in COPD, insomnia, and sleep deprivation. *Sleep Medicine Reviews*, *38*, 39–49. https://doi.org/10.1016/j.smrv.2017.03.005

Ong, J. L., Lo, J. C., Chee, N. I. Y. N., Santostasi, G., Paller, K. A., Zee, P. C., & Chee, M. W. L. (2016). Effects of phase-locked acoustic stimulation during a nap on EEG spectra and declarative memory consolidation. *Sleep Medicine*, *20*, 88–97. https://doi.org/10.1016/j.sleep.2015.10.016

Ooms, S., Overeem, S., Besse, K., Rikkert, M. O., Verbeek, M., & Claassen, J. A. (2014). Effect of 1 Night of Total Sleep Deprivation on Cerebrospinal Fluid beta-Amyloid 42 in Healthy Middle-Aged Men: A Randomized Clinical Trial. *JAMA Neurology*, *71*(8), 971-977. https://doi.org/10.1001/jamaneurol.2014.1173

Opalka, A. N., Huang, W.-Q., Liu, J., Liang, H., & Wang, D. V. (2020). Hippocampal ripple coordinates retrosplenial inhibitory neurons during slow-wave sleep. *Cell Reports*, *30*(2), 432-441.e3. https://doi.org/10.1016/j.celrep.2019.12.038

Oudiette, D., & Paller, K. A. (2013). Upgrading the sleeping brain with targeted memory reactivation. *Trends in Cognitive Sciences*, *17*(3), 142–149. https://doi.org/10.1016/j.tics.2013.01.006

Oyanedel, C. N., Durán, E., Niethard, N., Inostroza, M., & Born, J. (2020). Temporal associations between sleep slow oscillations, spindles and ripples. *The European Journal of Neuroscience*, *52*(12), 4762-4778. https://doi.org/10.1111/ejn.14906

Pachana, N. A., Byrne, G. J., Siddle, H., Koloski, N., Harley, E., & Arnold, E. (2007). Development and validation of the Geriatric Anxiety Inventory. *International Psychogeriatrics*, *19*(1), 103-114. https://doi.org/10.1017/S1041610206003504

Papalambros, N. A., Santostasi, G., Malkani, R. G., Braun, R., Weintraub, S., Paller, K. A., & Zee, P. C. (2017). Acoustic enhancement of sleep slow oscillations and concomitant memory improvement in older adults. *Frontiers in Human Neuroscience*, *11*, 109. https://doi.org/10.3389/fnhum.2017.00109

Penley, S. C., Hinman, J. R., Sabolek, H. R., Escabí, M. A., Markus, E. J., & Chrobak, J. J. (2012). Theta and gamma coherence across the septotemporal axis during distinct behavioral states. *Hippocampus*, *22*(5), 1164–1175. https://doi.org/10.1002/hipo.20962

Penttonen, M., & Buzsáki, G. (2003). Natural logarithmic relationship between brain oscillators. *Thalamus & Related Systems*, *2*(2), 145-152. https://doi.org/10.1017/s1472928803000074

Pereira, S. I. R., & Lewis, P. A. (2020). The differing roles of NREM and REM sleep in the slow enhancement of skills and schemas. *Current Opinion in Physiology*, *15*, 82–88. https://doi.org/10.1016/j.cophys.2019.12.005

Perrault, A. A., Khani, A., Quairiaux, C., Kompotis, K., Franken, P., Muhlethaler, M., Schwartz, S., & Bayer, L. (2019). Whole-night continuous rocking entrains spontaneous neural oscillations with benefits for sleep and memory. *Current Biology*, *29*(3), 402-411.e3. https://doi.org/10.1016/j.cub.2018.12.028

Peters, K. R., Ray, L., Smith, V., & Smith, C. (2008). Changes in the density of stage 2 sleep spindles following motor learning in young and older adults. *Journal of Sleep Research, 17,* 22-33 https://doi.org/10.1111/j.1365.2008.00634.x

Petersen, R. C. (2004). Mild cognitive impairment as a diagnostic entity. *Journal of Internal Medicine*, *256*(3), 183–194. https://doi.org/10.1111/j.1365-2796.2004.01388.x

Peyrache, A., Khamassi, M., Benchenane, K., Wiener, S. I., & Battaglia, F. P. (2009). Replay of rule-learning related neural patterns in the prefrontal cortex during sleep. *Nature Neuroscience*, *12*(7), 919–926. https://doi.org/10.1038/nn.2337

Pfurtscheller, G., & Cooper, R. (1975). Frequency dependence of the transmission of the EEG from cortex to scalp. *Electroencephalography and Clinical Neurophysiology*, *38*(1), 93–96. https://doi.org/10.1016/0013-4694(75)90215-1

Piantoni, G., Astill, R. G., Raymann, R. J. E. M., Vis, J. C., Coppens, J. E., & Someren, E. J. W. Van. (2013). Modulation of gamma and spindle-range power by slow oscillations in scalp sleep EEG of children. *International Journal of Psychophysiology*, *89*(2), 252–258. https://doi.org/10.1016/j.ijpsycho.2013.01.017

Pignatelli, M., Beyeler, A., & Leinekugel, X. (2012). Neural circuits underlying the generation of theta oscillations. *Journal of Physiology, 106,* 81-92. http://doi.org/10.1016/j.jphysparis.2011.09.007

Piosczyk, H., Holz, J., Feige, B., Spiegelhalder, K., Weber, F., Landmann, N., Kuhn, M., Frase, L., Riemann, D., Voderholzer, U., & Nissen, C. (2013). The effect of sleep-specific brain activity versus reduced stimulus interference on declarative memory consolidation. *Journal of Sleep Research*, *22*(4), 406–413. https://doi.org/10.1111/jsr.12033

Plihal, W., & Born, J. (1997). Effects of early and late nocturnal sleep on declarative and procedural memory. *Journal of Cognitive Neuroscience*, *9*(4), 534-547. https://doi.org/10.1162/jocn.1997.9.4.534

Popa, D., Duvarci, S., Popescu, A. T., Léna, C., & Paré, D. (2010). Coherent amygdalocortical theta promotes fear memory consolidation during paradoxical sleep. *Proceedings of the National Academy of Sciences of the United States of America*, *107*(14), 6516–6519. https://doi.org/10.1073/pnas.0913016107

Pope, K. J., Fitzgibbon, S. P., Lewis, T. W., Whitham, E. M., & Willoughby, J. O. (2009). Relation of gamma oscillations in scalp recordings to muscular activity. *Brain Topography*, *22*(1), 13–17. https://doi.org/10.1007/s10548-009-0081-x

Porter, V. R., Buxton, W. G., & Avidan, A. Y. (2015). Sleep, cognition and dementia. *Current Psychiatry Reports, 17,* 97. http://doi.org/10.1007/s11920-015-0631-8

Puentes-Mestril, C., Roach, J., Niethard, N., Zochowski, M., & Aton, S. J. (2019). How rhythms of the sleeping brain tune memory and synaptic plasticity. *Sleep*, *42*(7). https://doi.org/10.1093/sleep/zsz095

Purple, R. J., Cosgrave, J., Vyazovskiy, V., Foster, R. G., Porcheret, K., & Wulff, K. (2020). Sleep-related memory consolidation in the psychosis spectrum phenotype. *Neurobiology of Learning and Memory*, *174*(107273), 107273. https://doi.org/10.1016/j.nlm.2020.107273

Rabbitt, P. M. A., Ibrahim, S., Lunn, M., Scott, M., Thacker, N., Hutchinson, C., Horan, M., Pendleton, N., & Jackson, A. (2019). Age-associated losses of brain volume predict longitudinal cognitive declines over 8 to 20 years. In *Cognitive Development and the Ageing Process* (pp. 304–319). Routledge.

Rasch, B., & Born, J. (2013). About sleep's role in memory. *Physiological Reviews*, *93*(2), 681–766. https://doi.org/10.1152/physrev.00032.2012

Rasch, B., Büchel, C., Gais, S., & Born, J. (2007). Odor cues during slow-wave sleep prompt declarative memory consolidation. *Science*, *315*(5817), 1426–1429. https://doi.org/10.1126/science.1138581

Rauchs, G., Desgranges, B., Foret, J., & Eustache, F. (2005). The relationships between memory systems and sleep stages. *Journal of Sleep Research*, *14*(2), 123–140. https://doi.org/10.1111/j.1365-2869.2005.00450.x

Rauchs, G., Schabus, M., Parapatics, S., Bertran, F., Clochon, P., Hot, P., Denise, P., Desgranges, B., Eustache, F., Gruber, G., & Anderer, P. (2008). Is there a link between sleep changes and memory in Alzheimer's disease? *Neuroreport*, *19*(11), 1159–1162. https://doi.org/10.1097/WNR.0b013e32830867c4

Reid, K. J., Martinovich, Z., Finkel, S., Statsinger, J., Golden, R., Harter, K., & Zee, P. C. (2006). Sleep: a marker of physical and mental health in the elderly. *The American Journal of Geriatric Psychiatry*, *14*(10), 860–866. https://doi.org/10.1097/01.JGP.0000206164.56404.ba

Riedner, B. A., Vyazovskiy, V. V., Huber, R., Massimini, M., Esser, S., Murphy, M., & Tononi, G. (2007). Sleep homeostasis and cortical synchronization: III. A high-density EEG study of sleep slow waves in humans. *Sleep*, *30*(12), 1643–1657. https://doi.org/10.1093/sleep/30.12.1643

Rosanova, M., & Ulrich, D. (2005). Pattern-specific associative long-term potentiation induced by a sleep spindle-related spike train. *The Journal of Neuroscience*, *25*(41), 9398–9405. https://doi.org/10.1523/JNEUROSCI.2149-05.2005

Rossetti, H. C., Lacritz, L. H., Cullum, C. M., & Weiner, M. F. (2011). Normative data for the Montreal Cognitive Assessment (MoCA) in a population-based sample. *Neurology*, *77*(13), 1272-1275. https://doi.org/10.1212/WNL.0b013e318230208a

Ruch, S., Markes, O., Duss, S. B., Oppliger, D., Reber, T. P., Koenig, T., Mathis, J., Roth, C., & Henke, K. (2012). Sleep stage II contributes to the consolidation of declarative memories. *Neuropsychologia, 50*(10), 2389–2396. https://doi.org/10.1016/j.neuropsychologia.2012.06.008

Saletin, J. M., Goldstein, A. N., & Walker, M. P. (2011). The role of sleep in directed forgetting and remembering of human memories. *Cerebral Cortex*, *21*(11), 2534–2541. https://doi.org/10.1093/cercor/bhr034

Saletin, J. M., van der Helm, E., & Walker, M. P. (2013). Structural brain correlates of human sleep oscillations. *Neuroimage, 83,* 658-668. http://doi.org/10.1016/j.neuroimage.2013.06.021

Sanchez-Vives, M. V. & McCorick, D. A. (2000). Cellular and network mechanisms of rhythmic recurrent activity in neocortex. *Nature Neuroscience, 3,* 1027-1034. http://doi.org/10.1038/79848

Sattari, N., Whitehurst, L. N., Ahmadi, M., & Mednick, S. C. (2019). Does working memory improvement benefit from sleep in older adults? *Neurobiology of Sleep and Circadian Rhythms*, *6*, 53–61. https://doi.org/10.1016/j.nbscr.2019.01.001

Scarpelli, S., D'Atri, A., Bartolacci, C., Mangiaruga, A., Gorgoni, M., & De Gennaro, L. (2019). Oscillatory EEG activity during REM sleep in elderly people predicts subsequent dream recall after awakenings. *Frontiers in Neurology*, *10*, 985. https://doi.org/10.3389/fneur.2019.00985

Schabus, M., Dang-Vu, T. T., Heib, D. P. J., Boly, M., Desseilles, M., Vandewalle, G., Schmidt, C., Albouy, G., Darsaud, A., Gais, S., Degueldre, C., Balteau, E., Phillips, C., Luxen, A., & Maquet, P. (2012). The fate of incoming stimuli during NREM sleep is determined by spindles and the phase of the slow oscillation. *Frontiers in Neurology*, *3*, 40. https://doi.org/10.3389/fneur.2012.00040

Schabus, M., Gruber, G., Parapatics, S., Sauter, C., Klösch, G., Anderer, P., Klimesch, W., Saletu, B., & Zeitlhofer, J. (2004). Sleep spindles and their significance for declarative memory consolidation. *Sleep*, *27*(8), 1479–1485. https://doi.org/10.1093/sleep/27.7.1479

Schalkwijk, F. J., Sauter, C., Hoedlmoser, K., Heib, D. P. J., Klösch, G., Moser, D., Gruber, G., Anderer, P., Zeitlhofer, J., & Schabus, M. (2019). The effect of daytime napping and full-night sleep on the consolidation of declarative and procedural information. *Journal of Sleep Research*, *28*(1), e12649. https://doi.org/10.1111/jsr.12649

Scheffzük, C., Kukushka, V., I. Vyssotski, A. L., Draguhn, A., Tort, A. B. L. & Brankac, J., (2011). Selective coupling between theta phase and neocortical fast gamma oscillations during REM-sleep in mice. *PLoS ONE, 6*(12): e28489. http://doi.org/10.1371/journal.pone.0028489

Schneider, J., Lewis, P. A., Koester, D., Born, J., & Ngo, H. V. V. (2020). Susceptibility to auditory closed-loop stimulation of sleep slow oscillations changes with age. *Sleep*, *43*(12), 1-10. https://doi.org/10.1093/sleep/zsaa111

Schredl, M., Weber, B., Leins, M. L., & Heuser, I. (2001). Donepezil-induced REM sleep augmentation enhances memory performance in elderly, healthy persons. *Experimental Gerontology*, *36*(2), 353–361. https://doi.org/10.1016/s0531-5565(00)00206-0

Schreiner, T., Doeller, C. F., Jensen, O., Rasch, B., & Staudigl, T. (2018). Theta phase-coordinated memory reactivation reoccurs in a slow-oscillatory rhythm during NREM sleep. *Cell Reports*, *25*(2), 296–301. https://doi.org/10.1016/j.celrep.2018.09.037

Schreiner, T., Lehmann, M., & Rasch, B. (2015). Auditory feedback blocks memory benefits of cueing during sleep. *Nature Communications*, *6*(1), 1-11. http://doi.org/10.1038/ncomms9729

Schreiner, T., Petzka, M., Staudigl, T., & Staresina, B. P. (2021). Endogenous memory reactivation during sleep in humans is clocked by slow oscillation-spindle complexes. *Nature Communications*, *12*(1), 3112. https://doi.org/10.1038/s41467-021-23520-2

Schreiner, T. & Rasch, B. (2015). Boosting vocabulary learning by verbal cueing during sleep. *Cerebral Cortex, 25*(11), 4169-4179. http://doi.org/10.1093/cercor/bhu139.

Schreiner, T., & Staudigl, T. (2020). Electrophysiological signatures of memory reactivation in humans. *Philosophical Transactions of the Royal Society of London. Series B, Biological Sciences*, *375*(1799), 20190293. https://doi.org/10.1098/rstb.2019.0293

Scott, A. J., Webb, T. L., Martyn-St James, M., Rowse, G., & Weich, S. (2021). Improving sleep quality leads to better mental health: A meta-analysis of randomised controlled trials. *Sleep Medicine Reviews*, *60*(101556), 101556. https://doi.org/10.1016/j.smrv.2021.101556

Shekleton, J. A., Flynn-Evans, E. E., Miller, B., Epstein, L. J., Kirsch, D., Brogna, L. A., Burke, L. M., Bremer, E., Murray, J. M., Gehrman, P., Lockley, S. W., & Rajaratnam, S. M. W. (2014). Neurobehavioral performance impairment in insomnia: relationships with self-reported sleep and daytime functioning. *Sleep*, *37*(1), 107–116. https://doi.org/10.5665/sleep.3318

Shekleton, J. A., Rogers, N. L., & Rajaratnam, S. M. W. (2010). Searching for the daytime impairments of primary insomnia. *Sleep Medicine Reviews*, *14*(1), 47–60. https://doi.org/10.1016/j.smrv.2009.06.001

Shine, J. M., Handojoseno, A. M. A., Nguyen, T. N., Tran, Y., Naismith, S. L., Nguyen, H., & Lewis, S. J. G. (2014). Abnormal patterns of theta frequency oscillations during the temporal evolution of freezing of gait in Parkinson's disease. *Clinical Neurophysiology*, *125*(3), 569–576. https://doi.org/10.1016/j.clinph.2013.09.006

Shub, D., Darvishi, R., & Kunik, M. E. (2009). Non-pharmacologic treatment of insomnia in persons with dementia. *Geriatrics*, *64*(2), 22–26.

Siapas, A. G., & Wilson, M. A. (1998). Coordinated interactions between hippocampal ripples and cortical spindles during slow-wave sleep. *Neuron*, *21*(5), 1123–1128. https://doi.org/10.1016/s0896-6273(00)80629-7

Sigurdson, K., & Ayas, N. T. (2007). The public health and safety consequences of sleep disorders. *Canadian Journal of Physiology and Pharmacology*, *85*(1), 179–183. https://doi.org/10.1139/y06-095

Silber, M. H., Ancoli-Israel, S., Bonnet, M. H., Chokroverty, S., Grigg-Damberger, M. M., Hirshkowitz, M., Kapen, S., Keenan, S. A., Kryger, M. H., Penzel, T., Pressman, M. R., & Iber, C. (2007). The visual scoring of sleep in adults. *Journal of Clinical Sleep Medicine*, *03*(02), 121–131. https://doi.org/10.5664/jcsm.26814

Silva, G. E., Vana, K. D., Goodwin, J. L., Sherrill, D. L., & Quan, S. F. (2011). Identification of patients with sleep disordered breathing: comparing the four-variable screening tool, STOP, STOP-Bang, and Epworth Sleepiness Scales. *Journal of Clinical Sleep Medicine*, *7*(5), 467-472. https://doi.org/10.5664/JCSM.1308

Simor, P., Gombos, F., Szakadát, S., Sándor, P., & Bódizs, R. (2016). EEG spectral power in phasic and tonic REM sleep: different patterns in young adults and children. *Journal of Sleep Research*, 25(3), 269–277. https://doi.org/10.1111/jsr.12376

Simor, P., van der Wijk, G., Nobili, L., & Peigneux, P. (2020). The microstructure of REM sleep: Why phasic and tonic? *Sleep Medicine Reviews*, *52*(101305), 101305. https://doi.org/10.1016/j.smrv.2020.101305

Smith, C. T., Nixon, M. R., & Nader, R. S. (2004). Posttraining increases in REM sleep intensity implicate REM sleep in memory processing and provide a biological marker of learning potential. *Learning & Memory*, *11*(6), 714–719. https://doi.org/10.1101/lm.74904

Sopp, M. R., Michael, T., Weeß, H.-G., & Mecklinger, A. (2017). Remembering specific features of emotional events across time: The role of REM sleep and prefrontal theta oscillations. *Cognitive, Affective & Behavioral Neuroscience*, *17*(6), 1186–1209. https://doi.org/10.3758/s13415-017-0542-8

Spira, A. P., Gamaldo, A. A., An, Y., Wu, M. N., Simonsick, E. M., Bilgel, M. Zhou, Y., Wong, D. F., Ferrucci, L., & Resnick, S. M. (2013). Self-reported sleep and B-amyloid deposition in community-dwelling older adults. *JAMA Neurology, 70*(12), 1537-1543. http://doi.org/10.1001/jamaneurol.2013.4258

Srinivasan, R., Nunez, P. L., & Silberstein, R. B. (1998). Spatial filtering and neocortical dynamics: estimates of EEG coherence. *IEEE Transactions on Bio-Medical Engineering*, *45*(7), 814–826. https://doi.org/10.1109/10.686789

Stanley, N. (2005). The physiology of sleep and the impact of ageing. *European Urology Supplements*, *3*(6), 17–23. https://doi.org/10.1016/s1569-9056(05)80003-x

Staresina, B. P., Bergmann, T. O., Bonnefond, M., van der Meij, R., Jensen, O., Deuker, L., Elger, C. E., Axmacher, N., & Fell, J. (2015). Hierarchical nesting of slow oscillations, spindles and ripples in the human hippocampus during sleep. *Nature Neuroscience*, *18*(11), 1679–1686. https://doi.org/10.1038/nn.4119

Steiger, A. (2007). Neurochemical regulation of sleep. *Journal of Psychiatric Research*, *41*(7), 537-552. https://doi.org/10.1016/j.jpsychires.2006.04.007

Stein, M. B., Belik, S.-L., Jacobi, F., & Sareen, J. (2008). Impairment associated with sleep problems in the community: relationship to physical and mental health comorbidity. *Psychosomatic Medicine*, *70*(8), 913–919. https://doi.org/10.1097/PSY.0b013e3181871405

Steriade, M. (2001). Impact of network activities on neuronal properties in corticothalamic systems. *Journal of Neurophysiology*, *86*(1), 1–39. https://doi.org/10.1152/jn.2001.86.1.1

Steriade, M. (2003). The corticothalamic system in sleep. *Frontiers in Bioscience*, *8*(4), d878-99. https://doi.org/10.2741/1043

Steriade, M., Contreras, D., Curro Dossi, R., & Nunez, A. (1993). The slow (< 1 Hz) oscillation in reticular thalamic and thalamocortical neurons: Scenario of sleep rhythm generation in interacting thalamic and neocortical networks. *The Journal of Neuroscience, 13*(8), 3284-3299. https://doi.org/10.1523/jneurosci.13-08-03284.1993

Steriade, M., McCormick, D. A., & Sejnowski, T. J. (1993). Thalamocortical oscillations in the sleeping and aroused brain. *Science*, *262*(5134), 679–685. https://doi.org/10.1126/science.8235588

Steriade, M., Nunez, A., Amzica, F. (1993a). A novel slow (< 1 Hz) oscillation of neocortical neurons *in vivo*: Depolarizing and hyperpolarizing components. *The Journal of Neuroscience, 13,* 3252-3265. https://doi.org/10.1523/jneurosci.13-08-03252.1993

Steriade, M., Nunez, A., & Amzica, F. (1993b). Intracellular analysis of relations between the slow (< 1 Hz) neocortical oscillation and other sleep rhythms of the electroencephalogram. *The Journal of Neuroscience, 13*(8), 3266-3283. https://doi.org/10.1523/jneurosci.13-08-03266.1993

Stern, R. G., Mohs, R. C., Davidson, M., Schmeidler, J., Silverman, J., Kramer-Ginsberg, E., Searcey, T., Bierer, L., & Davis, K. L. (1994). A longitudinal study of Alzheimer's disease: measurement, rate, and predictors of cognitive deterioration. *The American Journal of Psychiatry*, *151*(3), 390–396. https://doi.org/10.1176/ajp.151.3.390

Stickgold, R., & Walker, M. P. (2005). Memory consolidation and reconsolidation: what is the role of sleep? *Trends in Neurosciences*, *28*(8), 408–415. https://doi.org/10.1016/j.tins.2005.06.004

Strauss, M., Griffon, L., Van Beers, P., Elbaz, M., Bouziotis, J., Sauvet, F., Chennaoui, M., Léger, D., & Peigneux, P. (2022). Order matters: sleep spindles contribute to memory consolidation only when followed by rapid-eye-movement sleep. *Sleep*, *45*(4). https://doi.org/10.1093/sleep/zsac022

Sullivan, D., Mizuseki, K., Sorgi, A., & Buzsaki, G. (2015). Comparison of sleep spindles and theta oscillations in the hippocampus. *The Journal of Neuroscience, 34*(2), 662-674 https://doi.org/10.1523/jneurosci.0552-13.2014

Sunwoo, J.-S., Cha, K. S., Byun, J.-I., Jun, J.-S., Kim, T.-J., Shin, J.-W., Lee, S.-T., Jung, K.-H., Park, K.-I., Chu, K., Kim, M., Lee, S. K., Kim, H.-J., Schenck, C. H., & Jung, K.-Y. (2021). Nonrapid eye movement sleep electroencephalographic oscillations in idiopathic rapid eye movement sleep behavior disorder: a study of sleep spindles and slow oscillations. *Sleep*, *44*(2). https://doi.org/10.1093/sleep/zsaa160

Swann, N. C., de Hemptinne, C., Aron, A. R., Ostrem, J. L., Knight, R. T., & Starr, P. A. (2015). Elevated synchrony in Parkinson disease detected with electroencephalography: Elevated Synchrony in PD. *Annals of Neurology*, *78*(5), 742–750. https://doi.org/10.1002/ana.24507

Tahmasian, M., Samea, F., Khazaie, H., Zarei, M., Kharabian Masouleh, S., Hoffstaedter, F., Camilleri, J., Kochunov, P., Yeo, B. T. T., Eickhoff, S. B., & Valk, S. L. (2020). The interrelation of sleep and mental and physical health is anchored in grey-matter neuroanatomy and under genetic control. *Communications Biology*, *3*(1), 171. https://doi.org/10.1038/s42003-020-0892-6

Taillard, J., Philip, P., Chastang, J. F., & Bioulac, B. (2004). Validation of Horne and Ostberg morningness-eveningness questionnaire in a middle-aged population of French workers. *Journal of Biological Rhythms*, *19*(1), 76-86. https://doi.org/10.1177/0748730403259849

Tamaki, M., Matsuoka, T., Nittono, H., & Hori, T. (2008). Fast sleep spindle (13-15 hz) activity correlates with sleep-dependent improvement in visuomotor performance. *Sleep*, *31*(2), 204–211. https://doi.org/10.1093/sleep/31.2.204

Tamaki, M., Wang, Z., Barnes-Diana, T., Guo, D., Berard, A. V., Walsh, E., Watanabe, T., & Sasaki, Y. (2020). Complementary contributions of non-REM and REM sleep to visual learning. *Nature Neuroscience*, *23*(9), 1150–1156. https://doi.org/10.1038/s41593-020-0666-y

Terzano, M. G., Parrino, L., Smerieri, A., Chervin, R., Chokroverty, S., Guilleminault, C., Hirshkowitz, M., Mahowald, M., Moldofsky, H., Rosa, A., Thomas, R., & Walters, A. (2002). Atlas, rules, and recording techniques for the scoring of cyclic alternating pattern (CAP) in human sleep. *Sleep Medicine*, *3*(2), 187–199. https://doi.org/10.1016/s1389-9457(02)00003-5

Timofeev, I., Grenier, F., Bazhenov, M., Sejnowski, T. J., & Steriade, M. (2000). Origin of slow cortical oscillations in deafferented cortical slabs. *Cerebral Cortex*, *10*(12), 1185–1199. https://doi.org/10.1093/cercor/10.12.1185

Timofeev, Igor, & Chauvette, S. (2011). Thalamocortical oscillations: local control of EEG slow waves. *Current Topics in Medicinal Chemistry*, *11*(19), 2457–2471. https://doi.org/10.2174/156802611797470376

Timofeev, I. & Steriade, M. (1996). Low-frequency rhythms in the thalamus of intact-cortex and decorticated cats. *Journal of Neurophysiology, 76*(6), 4152-4168. https://doi.org/10.1152/jn.1996.76.6.4152

Todorova, R., & Zugaro, M. (2020). Hippocampal ripples as a mode of communication with cortical and subcortical areas. *Hippocampus*, *30*(1), 39-49. https://doi.org/10.1002/hipo.22997

Tombaugh, T. N., & McIntyre, N. J. (1992). The mini-mental state examination: A comprehensive review. *Journal of the American Geriatrics Society*, *40*(9), 922-935. https://doi.org/10.1111/j.1532-5415.1992.tb01992.x

Tort, A. B., Komorowski, R., Eichenbaum, H., & Kopell, N. (2010). Measuring phase-amplitude coupling between neuronal oscillations of different frequencies. *Journal of Neurophysiology*, *104*(2), 1195-1210. https://doi.org/10.1152/jn.00106.2010

Tort, A. B., Scheffer-Teixeira, R., Souza, B. C., Draguhn, A., & Brankack, J. (2013). Theta-associated high-frequency oscillations (110-160 Hz) in the hippocampus and neocortex. *Progress in Neurobiology, 100,* 1-14. https://doi.org/10.1016/j.pneurobio.2012.09.002

Ulrich, D. (2016). Sleep spindles as facilitators of memory formation and learning. *Neural Plasticity*, *2016*, 1796715. https://doi.org/10.1155/2016/1796715

Ujma, P. P., Gombos, F., Genzel, L., Konrad, B. N., Simor, P., Steiger, A., Dresler, M., & Bódizs, R. (2015). A comparison of two sleep spindle detection methods based on all night averages: individually adjusted vs. fixed frequencies. *Frontiers in Human Neuroscience*, *9*, 52. https://doi.org/10.3389/fnhum.2015.00052

Urakami, Y., Ioannides, A. A., & Kostopoulos, G. K. (2012). *Sleep Spindles-As a biomarker of brain function and plasticity*. In Ajeena, I. M. (Ed.), *Advances in Clinical Neurophysiology* (Vol. 4, pp. 73-108). InTech. https://doi.org/10.5772/48427

Valderrama, M., Crépon, B., Botella-Soler, V., Martinerie, J., Hasboun, D., Alvarado-Rojas, C., Baulac, M., Adam, C., Navarro, V., & Le Van Quyen, M. (2012). Human gamma oscillations during slow wave sleep. *PloS One*, *7*(4), e33477. https://doi.org/10.1371/journal.pone.0033477

Valencia, M., Artieda, J., Bolam, J. P., & Mena-Segovia, J. (2013). Dynamic interaction of spindles and gamma activity during cortical slow oscillations and its modulation by subcortical afferents. *PloS One*, *8*(7), e67540. https://doi.org/10.1371/journal.pone.0067540

Van Egroo, M., Narbutas, J., Chylinski, D., Villar González, P., Maquet, P., Salmon, E., Bastin, C., Collette, F., & Vandewalle, G. (2019). Sleep–wake regulation and the hallmarks of the pathogenesis of Alzheimer's disease. *Sleep*, *42*(4). https://doi.org/10.1093/sleep/zsz017

van Wijk, B. C. M., Beudel, M., Jha, A., Oswal, A., Foltynie, T., Hariz, M. I., Limousin, P., Zrinzo, L., Aziz, T. Z., Green, A. L., Brown, P., & Litvak, V. (2016). Subthalamic nucleus phase-amplitude coupling correlates with motor impairment in Parkinson's disease. *Clinical Neurophysiology*, *127*(4), 2010–2019. https://doi.org/10.1016/j.clinph.2016.01.015

Vertes, R. P. (2011). Hippocampal theta rhythm of REM sleep. In B. N. Mallick, S. R. Pandi-Perumal, R. W. McCarley, & A. R. Morrison (Eds.), *Rapid Eye Movement Sleep* (pp. 151–163). Cambridge University Press.

Viña, J., Borrás, C., & Miquel, J. (2007). Theories of ageing. *IUBMB Life*, *59*(4–5), 249–254. https://doi.org/10.1080/15216540601178067

Vyazovskiy, V. V., Riedner, B. A., Cirelli, C., & Tononi, G. (2007). Sleep homeostasis and cortical synchronization: II. A local field potential study of sleep slow waves in the rat. *Sleep*, *30*(12), 1631–1642. https://doi.org/10.1093/sleep/30.12.1631

Vysata, O., Kukal, J., Prochazka, A., Pazdera, L., & Valis, M. (2012). Age-related changes in the energy and spectral composition of EEG. *Neurophysiology*, *44*(1), 63-67. https://doi.org/10.1007/s11062-012-9268-y

Wagner, U., Gais, S., & Born, J. (2001). Emotional memory formation is enhanced across sleep intervals with high amounts of rapid eye movement sleep. *Learning & Memory*, *8*(2), 112–119. https://doi.org/10.1101/lm.36801

Walker, M. P. (2009). The role of sleep in cognition and emotion. *Annals of the New York Academy of Sciences*, *1156*(1), 168–197. https://doi.org/10.1111/j.1749-6632.2009.04416.x

Walker, M. P., & Stickgold, R. (2004). Sleep-dependent learning and memory consolidation. *Neuron*, *44*(1), 121–133. https://doi.org/10.1016/j.neuron.2004.08.031

Wang, C., & Holtzman, D. M. (2020). Bidirectional relationship between sleep and Alzheimer's disease: role of amyloid, tau, and other factors. *Neuropsychopharmacology*, *45*(1), 104–120. https://doi.org/10.1038/s41386-019-0478-5

Wang, X., Cheng, S., & Xu, H. (2019). Systematic review and meta-analysis of the relationship between sleep disorders and suicidal behaviour in patients with depression. *BMC Psychiatry*, *19*(1), 303. https://doi.org/10.1186/s12888-019-2302-5

Warriner, A. B., Kuperman, V., & Brysbaert, M. (2013). Norms of valence, arousal, and dominance for 13,915 English lemmas. *Behavior Research Methods*, *45*(4), 1191–1207. https://doi.org/10.3758/s13428-012-0314-x

Waterman, D., Elton, M., Hofman, W., Woestenburg, J. C., & Kok, A. (1993). EEG spectral power analysis of phasic and tonic REM sleep in young and older male subjects. *Journal of Sleep Research*, *2*(1), 21–27. https://doi.org/10.1111/j.1365-2869.1993.tb00056.x

Watson, G. S., & Williams, E. J. (1956). On the construction of significance tests on the circle and the sphere. *Biometrika*, *43*, 344–352. https://doi.org/10.2307/2332913

Webb, W. B. (1982). Sleep in older persons: sleep structures of 50- to 60-year-old men and women. *Journal of Gerontology*, *37*(5), 581–586. https://doi.org/10.1093/geronj/37.5.581

Webb, W. B., & Dreblow, L. M. (1982). A modified method for scoring slow wave sleep of older subjects. *Sleep*, *5*(2), 195-199. https://doi.org/10.1093/sleep/5.2.195

Wehrle, R., Kaufmann, C., Wetter, T. C., Holsboer, F., Auer, D. P., Pollmächer, T., & Czisch, M. (2007). Functional microstates within human REM sleep: first evidence from fMRI of a thalamocortical network specific for phasic REM periods: Thalamocortical network in phasic REM sleep. *The European Journal of Neuroscience*, *25*(3), 863–871. https://doi.org/10.1111/j.1460-9568.2007.05314.x

Weiner, O. M., & Dang-Vu, T. T. (2016). Spindle oscillations in sleep disorders: A systematic review. *Neural Plasticity*, *2016*, 7328725. https://doi.org/10.1155/2016/7328725

Weiner, O. M., O'Byrne, J., Cross, N. E., Giraud, J., Tarelli, L., Yue, V., Homer, L., Walker, K., Carbone, R., & Dang-Vu, T. T. (2023). Slow oscillation-spindle cross-frequency coupling predicts overnight declarative memory consolidation in older adults. *The European Journal of Neuroscience*. https://doi.org/10.1111/ejn.15980

Weissman, M. M., Greenwald, S., Nino-Murcia, G., & Dement, W. C. (1997). The morbidity of insomnia uncomplicated by psychiatric disorders. *General Hospital Psychiatry, 19*(4), 245-250. http://doi.org/10.1016/S0163-8343(97)00056-X

Weng, Y.-Y., Lei, X., & Yu, J. (2020). Sleep spindle abnormalities related to Alzheimer's disease: a systematic mini-review. *Sleep Medicine*, *75*, 37–44. https://doi.org/10.1016/j.sleep.2020.07.044

Werth, E., Achermann, P., Dijk, D. J., & Borbély, A. A. (1997). Spindle frequency activity in the sleep EEG: Individual differences and topographic distribution. *Electroencephalography and Clinical Neurophysiology, 103*(5), 535-542. https://doi.org/10.1016/s0013-4694(97)00070-9

Westerberg, C. E., Mander, B. A., Florczak, S. M., Weintraub, S., Mesulam, M. M., Zee, P. C., & Paller, K. A. (2012). Concurrent impairments in sleep and memory in amnestic mild cognitive impairment. *Journal of the International Neurophychological Society, 18*(3), 490-500. http://doi.org/10.1017/S135561771200001X

Wetter, T. C., Beitinger, P. A., Beitinger, M. E., & Wollweber, B. (2010). Pathophysiology of sleep disorders. In *GABA and Sleep* (pp. 325–361). Springer Basel.

Whitham, E. M., Pope, K. J., Fitzgibbon, S. P., Lewis, T., Clark, C. R., Loveless, S., Broberg, M., Wallace, A., DeLosAngeles, D., Lillie, P., Hardy, A., Fronsko, R., Pulbrook, A., & Willoughby, J. O. (2007). Scalp electrical recording during paralysis: quantitative evidence that EEG frequencies above 20 Hz are contaminated by EMG. *Clinical Neurophysiology*, *118*(8), 1877–1888. https://doi.org/10.1016/j.clinph.2007.04.027

Wilson, J. K., Baran, B., Pace-Schott, E. F., Ivry, R. B., & Spencer, R. M. C. (2012). Sleep modulates word-pair learning but not motor sequence learning in healthy older adults. *Neurobiology of Aging*, *33*(5), 991–1000. https://doi.org/10.1016/j.neurobiolaging.2011.06.029

Winer, J. R., Mander, B. A., Helfrich, R. F., Maass, A., Harrison, T. M., Baker, S. L., Knight, R. T., Jagust, W. J., & Walker, M. P. (2019). Sleep as a potential biomarker of tau and β-amyloid burden in the human brain. *The Journal of Neuroscience*, *39*(32), 6315–6324. https://doi.org/10.1523/JNEUROSCI.0503-19.2019

Womelsdorf, T., Schoffelen, J.-M., Oostenveld, R., Singer, W., Desimone, R., Engel, A. K., & Fries, P. (2007). Modulation of neuronal interactions through neuronal synchronization. *Science*, *316*(5831), 1609–1612. https://doi.org/10.1126/science.1139597

Xie, L., Kang, H., Xu, Q., Chen, M. J., Liao, Y., Thiyagarajan, M., O'Donnell, J., Christensen, D. J., Nicholson, C., Iliff, J. J., Takano, T., Deane, R., & Nedergaard, M. (2013). Sleep drives metabolite clearance from the adult brain. *Science*, *342*(6156), 373–377. https://doi.org/10.1126/science.1241224

Yao, C. W., Pelletier, A., Fereshtehnejad, S.-M., Cross, N., Dang-Vu, T., & Postuma, R. B. (2022). Insomnia symptom subtypes and manifestations of prodromal neurodegeneration: a population-based study in the Canadian Longitudinal Study on Aging. *Journal of Clinical Sleep Medicine, 18*(2), 345–359. https://doi.org/10.5664/jcsm.9562

Yesavage, J. A., Brink, T. L., Rose, T. L., Lum, O., Huang, V., Adey, M., & Leirer, V. O. (1982). Development and validation of a geriatric depression screening scale: A preliminary report. *Journal of Psychiatric Research*, *17*(1), 37-49. https://doi.org/10.1016/0022-3956(82)90033-4

Yordanova, J., Kirov, R., Verleger, R., & Kolev, V. (2017). Dynamic coupling between slow waves and sleep spindles during slow wave sleep in humans is modulated by functional pre-sleep activation. *Scientific Reports*, *7*(1), 1–14. https://doi.org/10.1038/s41598-017-15195-x

Yuval-Greenberg, S., Tomer, O., Keren, A. S., Nelken, I., & Deouell, L. Y. (2008). Transient induced gamma-band response in EEG as a manifestation of miniature saccades. *Neuron, 58*(3), 429-441. http://doi.org/10.1016/j.neuron.2008.03.027

Zaninotto, P., Batty, G. D., Allerhand, M., & Deary, I. J. (2018). Cognitive function trajectories and their determinants in older people: 8 years of follow-up in the English Longitudinal Study of Ageing. *Journal of Epidemiology and Community Health*, *72*(8), 685–694. https://doi.org/10.1136/jech-2017-210116

Zhang, H., Fell, J., & Axmacher, N. (2018). Electrophysiological mechanisms of human memory consolidation. *Nature Communications*, *9*(1), 4103. https://doi.org/10.1038/s41467-018-06553-y

Zhang, Y., Ren, R., Yang, L., Zhang, H., Shi, Y., Okhravi, H. R., Vitiello, M. V., Sanford, L. D., & Tang, X. (2022). Sleep in Alzheimer's disease: a systematic review and meta-analysis of polysomnographic findings. *Translational Psychiatry*, *12*(1), 136. https://doi.org/10.1038/s41398-022-01897-y

Zhang, J., Yetton, B., Whitehurst, L. N., Naji, M., & Mednick, S. C. (2020). The effect of zolpidem on memory consolidation over a night of sleep. *Sleep*, *43*(11). https://doi.org/10.1093/sleep/zsaa084

Zhao, J.-L., Cross, N., Yao, C. W., Carrier, J., Postuma, R. B., Gosselin, N., Kakinami, L., & Dang-Vu, T. T. (2022). Insomnia disorder increases the risk of subjective memory decline in middle-aged and older adults: a longitudinal analysis of the Canadian Longitudinal Study on Aging. *Sleep*, *45*(11). https://doi.org/10.1093/sleep/zsac176

Zielinski, M. C., Shin, J. D., & Jadhav, S. P. (2021). Hippocampal theta sequences in REM sleep during spatial learning. In *bioRxiv*. https://doi.org/10.1101/2021.04.15.439854

Züst, M. A., Ruch, S., Wiest, R., & Henke, K. (2019). Implicit vocabulary learning during sleep is bound to slow-wave peaks. *Current Biology*, *29*(4), 541-553.e7. https://doi.org/10.1016/j.cub.2018.12.038

Appendix 1: Expanded Description of Sleep Stages, Cardinal Oscillations, and Related Mechanisms

NREM Sleep

During relaxed wakefulness and the transition to sleep, a sinusoidal alpha rhythm is present (8–13 Hz; 20–40 μV; Constant & Sabourdin, 2012). N1, or light sleep, is characterized by slow eye movements; vertex sharp wave oscillations (50–200 ms duration, up to 250 μV); and, low amplitude, mixed frequency activity in the theta range (4–7 Hz; 50–100 μV), most prominent over frontal midline regions (Iber et al., 2007; Terzano et al., 2002). Theta can be detected from multiple anatomical sites in both cortical and subcortical regions and may reflect the summative activity from multiple brain regions across different conscious states. The exact mechanisms of theta rhythm generation is not fully clear (Colgin, 2013; Nuñez & Buño, 2021; Vertes, 2011), however their generation may be mediated by excitatory and inhibitory pathways associated with the entorhinal cortex (Cantero et al., 2003; Pignatelli et al., 2012; Sullivan et al., 2015).

N2 sleep is characterized by K-complexes and sleep spindles. K-complexes, which can be spontaneous or evoked, are slow, high-amplitude delta waves (0.5–3 Hz, typically 100–400 μV over frontal derivations) lasting at least 0.5 sec (Iber et al., 2007; Silber et al., 2007). Sleep spindles (11–16 Hz) are trains of oscillations which wax and wane in amplitude, and last 0.5 to 3 sec (Iber et al., 2007). Spindles can be detected on EEG visually or using event-detection algorithms or measured in terms of spectral EEG power in the "sigma" band, reported as a proxy for spindle activity. The density of spindle activity typically follows a U-shaped curve within each sleep cycle, and shows a linear increase across successive sleep cycles (De Gennaro & Ferrara, 2003; Dijk et al., 1993; Himanen et al., 2002; Steriade, 2003; Sullivan et al., 2015). Sleep spindles are highly stable within persons, and particularly in relation to spindle amplitude (Eggert et al., 2015).

Spindle activity is attributed to interactions between thalamic reticular, thalamo-cortical (TC), and cortical pyramidal networks (Dang-Vu et al., 2011; Steriade, McCormick, & Sejnowsky, 1993). Spindle sequences occur when rhythmic bursts of inhibitory postsynaptic potentials (IPSP) are transmitted from GABAergic thalamic reticular to glutamatergic TC neurons. When large and long

enough, these IPSPs result in the de-inactivation of a low-threshold Ca^{2+} current. This produces spike bursts consisting of fast Na^{+}-mediated action potentials, which are transferred to cortical neurons where excitatory postsynaptic potentials (EPSPs) lead to action potentials, and therefore spindle sequences visible on the EEG. Cortical neurons then provide excitatory feedback to GABAergic thalamic reticular neurons, which restarts the spindle sequence (Jensen et al., 2014; Lüthi, 2014; Steriade, 2003; Urakami et al., 2012). Sleep spindles can be further subdivided into slow (< 13 Hz) and fast (> 13 Hz) spindles, which are prominent across frontal and centro-parietal regions, respectively. Sleep spindle activity is also known to vary across various sleep disorder sub-groups (e.g., insomnia, sleep apnea, narcolepsy; see Weiner & Dang-Vu 2016 for a systematic review).

N3, or slow-wave sleep (SWS), typically dominates the first half of sleep time, is associated with sleep homeostasis (Dang-Vu et al., 2011), and is characterized by low-frequency (1–4 Hz), high-amplitude ($\geq$ 75 μV) delta waves, observed in > 20% of an EEG epoch (Iber et al., 2007). Delta waves (1–4 Hz) can originate from both thalamic and cortical networks, though their mechanisms of generation in the cortex are less well understood (Cairney et al., 2015; Cole & Voytek, 2017; Steriade, 2003; Steriade, McCormick, & Sejnowsky, 1993; Timofeev & Chauvette, 2011). The stereotypical, prolonged depolarized-to-hyperpolarized oscillation activity is reflected in neural firing patterns of thalamic reticular (GABAergic) neurons, and feedback across various cortico-thalamo-cortical loops (Cox, Hofman et al., 2014; Dang-Vu, 2012; Feld et al., 2013). EEG delta waves predominate in frontal brain regions, propagate along an anterior-posterior axis (Cairney et al., 2015; Dang-Vu, 2012), and their amplitude is positively correlated with grey matter volume in the medial prefrontal (orbitofrontal, midline cingulate) cortex (Saletin et al., 2013).

In addition to spindles and delta, NREM sleep is also characterized by a cortical slow oscillation (< 1 Hz; > 140 μV). This slow oscillation (SO), observed in animals (Steirade, 2001) and humans (Achermann & Borbely, 1997), occurs when large assemblies of cortical neurons collectively vacillate between a prolonged depolarized state, consisting of non-NMDA-mediated EPSPs, fast pre-potentials, a voltage-dependent Na+ current, and GABAergic-mediated fast IPSPs, and a prolonged hyperpolarization

phase, resulting from mass removal of synaptic, mainly excitatory, inputs (Steriade, 2003). Like delta waves, the SO can be observed across cortical areas, but is most prominent in frontal brain regions (e.g., Dang-Vu et al., 2008), and they propagate across the cortex in an anteroposterior direction, likely via corticocortical network connections (Massimini et al., 2004). However, there is evidence from several studies that delta waves and SOs are distinct oscillatory phenomena, reflected by differences in phase-relationships and timing between the two (Steriade et al., 1993a and 1993b), power dynamics across sleep time (Achermann & Borbely, 1997), distinct neuroanatomical correlates (Dang-Vu et al., 2008), and associations with memory (i.e., remembering vs. forgetting; Kim et al., 2019). SOs are primarily generated in the neocortex (Amzica & Steriade, 1995; Sanchez-Vives & McCormick, 2000; Steriade et al., 1993a; Timofeev et al., 2000; Timofeev & Steriade, 1996), but have also been detected in the HC (Cox et al., 2020). Further, the thalamus may be involved in responding to and modulating cortical SO activity (Contreras & Steriade, 1995; Steriade et al., 1993a).

Another prominent oscillation observed during sleep is the sharp-wave ripple. A sharp-wave is produced when excitatory bursts from hippocampal (HC) CA3 cells induce a strong depolarization of CA1 pyramidal cells, and the resulting CA1-CA3 interaction induces a fast-frequency ripple event (80–100 or 200 Hz) in CA1 (Girardeau & Zugaro, 2011; see also Jiang et al., 2019a and 2019b). Ripples have also been observed from direct cortical recordings (Khodagholy et al., 2017), and they share similar characteristics (e.g., duration, frequency) with HC ripples (Dickey et al., 2021). Ripple activity is present in both sleep and quiet (inactive) wake periods (Todorova & Zugaro, 2020), with relatively more ripple activity during sleep, as shown both in rats (Opalka et al., 2020) and in humans (Dickey et al., 2021). Ripples are prominent during slow-wave-sleep (Dickey et al., 2021; Eschenko et al., 2008) and thought to reflect “offline” neural traces of wakeful experiences (Cross et al., 2018; Le Van Quyen et al., 2010; Piantoni et al., 2013; Valderrama et al., 2012). Importantly, ripples are most directly examined using intracranial or depth recording electrodes, and so most studies of ripple activity in humans are conducted on patients with epilepsy who are undergoing routine evaluation or other kind of surgical procedure.

REM Sleep

REM sleep is characterized by the presence of rapid eye movements (REMs), general muscle atonia, "saw tooth" brain waves (triangular, often serrated, centrally-maximal 2–6 Hz waves), and low amplitude, mixed frequency activity that resembles relaxed wakefulness or N1 sleep (Iber et al., 2007). REM sleep is divided into tonic (absent REMs) and phasic (present REMs) periods; there may be functional differences between these two sub-states, however available evidence for this is mixed (Brankačk et al., 2012; Cantero et al., 2000; Simor et al., 2016 and 2020; Wehrle et al., 2007). The onset and maintenance of REM sleep is determined by REM-ON and REM-OFF cell populations that are mediated, in part, by cholinergic, glutamatergic, and GABAergic neurotransmission (Luppi et al., 2012), as well as serotonergic and noradrenergic transmission across tegmental nucli and reticular formation regions (McKenna et al., 2017). Cholinergic firing before and during REM sleep helps to promote ponto-geniculo-occipital (PGO) waves, HC theta activity, and general muscle atonia (McKenna et al., 2017).

Prominent oscillatory activity in the theta (e.g., 4–7 Hz) and gamma (e.g., 20–100 Hz) bands is observed during REM in both animals and humans, and in both cortical and subcortical recordings (Bjorness et al., 2018; Brankack et al., 2012; Corsi-Cabrera et al., 2014; Montgomery et al., 2008; Nishida et al., 2004). Cantero and colleagues (2003) argued that the HC is primarily involved in the generation of theta activity bursts during REM sleep; as well, there is a positive correlation between theta phase and peak frequency in the statum radiatum of the CA1 region (Leung, 1984). There is some evidence that REM sleep theta activity reflects its own homeostatic process, both from studies with rats examining across-night changes (Bjorness et al., 2018) and with humans after sleep deprivation (Borbély et al., 1984). Oscillatory activity may be further distinguished between tonic and phasic REM sleep periods, such as evidence for greater theta and gamma activity in phasic versus tonic REM sleep in dentate, CA3, and CA1 HC regions (Montgomery et al., 2008). Gamma frequency activity (40–100 Hz) has also been detected in the rat HC and is similarly coherent with theta activity in the same regions between awake and REM sleep states (Penley et al., 2012).

Appendix 2: Published Review of Sleep Spindle Activity in Sleep Disorder Populations

Spindle Oscillations in Sleep Disorders: A Systematic Review

Oren M. Weiner[1,2] and Thien Thanh Dang-Vu[1,2,3]

[1]PERFORM Centre and Center for Studies in Behavioural Neurobiology, Department of Psychology and Department of Health, Kinesiology, and Applied Physiology, Concordia University, Montréal, Quebec, Canada

[2]Centre de Recherche de l'Institut Universitaire de Gériatrie de Montréal, CIUSSS Centre-Sud-de-l'île-de-Montréal, Montréal, Quebec, Canada

[3]Department of Neurosciences, Université de Montréal, Montréal, Quebec, Canada

Manuscript Published in *Neural Plasticity*

doi: http://dx.doi.org/10.1155/2016/7328725

Please refer to the journal's website for access to the original publication