**Fachbereich Erziehungswissenschaft und Psychologie**

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# Sleep-Associated Consolidation of Episodic Memories in Old Age – The Challenge of Studying Cognitive and Cerebral Aging

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## Eidesstattliche Erklärung

Hiermit versichere ich, dass ich die vorgelegte Arbeit selbstständig verfasst habe. Andere als die angegebenen Hilfsmittel habe ich nicht verwendet. Die Arbeit ist in keinem früheren Promotionsverfahren angenommen oder abgelehnt worden.

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.....

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## Summary

This dissertation pursues the objective to identify the neural mechanisms that drive the association between sleep and episodic memory consolidation across the adult lifespan. The inherent lifelong dynamics of brain and cognition provide an enormous potential to understand the neurobiological underpinnings of cognitive functions. Within this dissertation, aging is investigated as an illustrative period of cognitive and neural reorganization. Sleep-associated episodic memory consolidation is chosen as a model to illustrate methodological intricacies and highlight scientific gains that emerge when applying a lifespan perspective on cognitive neuroscience.

This dissertation consists of four publications that offer a theoretical and empirical perspective on sleep-associated consolidation of episodic memories in old age. *Paper I* integrates the currently available literature on sleep, episodic memory, and aging, and links it to the active system consolidation account. Within this theoretical framework, we describe how, by the concerted interplay of brain rhythms during non-rapid eye movement (NREM) sleep, recently encoded memories become integrated into long-term storage sites in the neocortex. Joint age-related alterations in NREM sleep, brain structure, function, and neurochemistry are hypothesized to result in the formation of less persistent memory traces during sleep. *Paper II* argues that studying these changes in sleep physiology during aging requires the development of age-fair and individualized analytic procedures. *Paper III* complements this view by the use of an age-adapted associative memory task. The article highlights that variation in the encoding quality of memories can account for divergent effects of aging on overnight memory consolidation. Patterns of NREM sleep physiology and brain structure – identified as characteristic for advancing age by the use of multivariate statistical tools – were associated with age-related impairments in memory consolidation. However, I demonstrate that the mere occurrence of slow oscillations and spindles, indicative of NREM sleep and memory consolidation, does not explain inter-individual differences in memory consolidation. Following up on this notion, in *Paper IV*, I take the temporal coordination of slow oscillation and sleep spindles into account and show that their precise coupling disperses in old age. Across age groups, a precise coordination of slow oscillations and spindles was associated with better memory consolidation. Moreover, in older age, maintained structural integrity in sleep- and memory-relevant brain areas reinforced this beneficial slow oscillation–spindle coupling.

Taken together, the findings of this dissertation suggest that prominent age-related changes in NREM sleep physiology may constitute a potential causal pathway for consolidation deficits observed in old age. In conjunction with structural brain atrophy, the generation and coordination of slow oscillation and spindles during NREM sleep is impacted, and the processes necessary to render stable episodic memories are impaired.

Overall, this dissertation accomplishes two main goals: First, it reveals novel methodological avenues to derive and link age-fair and sensitive sleep and memory measures. Second, based on this, this dissertation enriches traditional views on sleep-associated memory consolidation and advances our understanding of memory aging, in general. Certainly, the application of an aging perspective to cognitive neuroscience challenges research theoretically, practically, and methodologically. I am confident that facing these challenges is worth the effort, as studying cognitive aging and its neural correlates holds exceptional scientific promise.

## Zusammenfassung

Hauptziel dieser Dissertation ist die Identifikation neuronaler Mechanismen, die den Zusammenhang zwischen Schlaf und der Konsolidierung episodischer Gedächtnisinhalte im Erwachsenenalter vermitteln. Die lebenslangen Dynamik von Gehirn und Kognition birgt ein einzigartiges Potential, neurobiologische Grundlagen kognitiver Funktionen zu verstehen. In dieser Dissertation wurde das Alter als beispielhafte Phase kognitiver und neuronaler Veränderungen untersucht. Gedächtniskonsolidierung wurde als Musterbeispiel gewählt, um die methodischen Herausforderungen und den wissenschaftlichen Erkenntnisgewinn zu veranschaulichen, die durch die Einnahme einer Lebensspannenperspektive in den kognitiven Neurowissenschaften entstehen.

Diese Dissertation besteht aus vier Publikationen, die eine theoretische und empirische Sichtweise auf die Konsolidierung episodischer Gedächtnisinhalte im Alter bieten. *Artikel I* fasst die derzeitig verfügbare Literatur über Schlaf und episodisches Gedächtnis im Alter zusammen und setzt sie mit der Theorie der aktiven systemischen Konsolidierung in Verbindung. Im Rahmen dieser beschreiben wir, wie kürzlich Erlerntes durch das Zusammenspiel neuronaler Rhythmen im *non-rapid eye movement* (NREM) Schlaf in neokortikale Langzeitspeicher integriert wird. Es wird vermutet, dass altersbedingte Veränderungen im NREM-Schlaf, der Hirnstruktur und -funktion sowie der Neuromodulation zur Bildung weniger beständiger Gedächtnisspuren führen. *Artikel II* diskutiert, dass dem Alter angepasste und individualisierte Analyseansätze notwendig sind, um Alterungsprozesse des Schlafes zu untersuchen. *Artikel III* komplementiert diese Sichtweise indem er eine assoziative Gedächtnisaufgabe nutzt, die auf das Alter der Versuchsteilnehmer abgestimmt ist. Wir zeigen, dass Unterschiede in der Lernqualität von Gedächtnisinhalten verschiedenartige Alterseffekte in der nächtlichen Konsolidierung erklären können. Mittels multivariater statistischer Verfahren wurden bestimmte Muster der Schlafphysiologie und der Hirnstruktur als charakteristisch für zunehmendes Alter identifiziert und mit schlechterer Gedächtniskonsolidierung in Zusammenhang gebracht. Allerdings zeigte sich, dass das alleinige Auftreten langsamer Oszillationen und Spindeln, essentielle Elemente des NREM-Schlafes und der Konsolidierung, nicht ausschlaggebend für inter-individuelle Unterschiede in der Gedächtniskonsolidierung ist. Deswegen berücksichtige ich in *Artikel IV* das zeitliche Zusammenspiel langsamer Oszillationen und Spindeln und zeige, dass sich deren präzise Koordination im Alter verschiebt. Unabhängig vom Alter ist zu erkennen, dass eine präzise Koordination langsamer Oszillationen und Spindeln mit besserer Gedächtniskonsolidierung zusammenhängt. Darüber hinaus können ältere Menschen mit intakter Hirnstruktur in schlaf- und gedächtnisrelevanten Regionen dieses wirksame oszillatorische Kopplungsmuster aufrechterhalten.

Insgesamt legt meine Dissertation nahe, dass starke altersbedingte Veränderungen in der Physiologie des NREM-Schlafes einen möglichen Erklärungsmechanismus für Defizite in der Gedächtniskonsolidierung darstellen. Durch strukturelle Hirnatrophie ist die Entstehung und Koordination langsamer Oszillationen und Schlafspindeln im NREM-Schlaf eingeschränkt und die erforderlichen Prozesse zum Festigen episodischer Gedächtnisinhalte beeinträchtigt.

Insgesamt erreicht diese Dissertation zwei grundlegende Ziele: Sie zeigt neue methodische Wege auf, um altersangepasste und differenzierte Schlaf- und Gedächtnismaße abzuleiten und miteinander in Verbindung zu setzen. Darauf basierend bereichert diese Arbeit traditionelle Sichtweisen der Gedächtniskonsolidierung und -alterung. In der Altersforschung wird man zweifellos mit vielfältigen Herausforderungen konfrontiert. Ich bin jedoch sicher, dass man sich diesen theoretischen, praktischen und methodischen Hindernissen stellen sollte, denn die Untersuchung kognitiver und neuronaler Alterungsprozesse verspricht einen einmaligen wissenschaftlichen Erkenntnisgewinn.

## List of Publications

**Paper I**

**Muehlroth, B. E.**, Rasch, B., & Werkle-Bergner, M. (under review). *Episodic memory consolidation during sleep in healthy aging*.

**Paper II**

**Muehlroth, B. E.**, & Werkle-Bergner, M. (2019). Studying the interplay of sleep and aging: Methodological challenges. *bioRxiv,* 713552. doi: 10.1101/713552.

**Paper III**

**Muehlroth, B. E.**, Sander, M. C., Fandakova, Y., Grandy, T. H., Rasch, B., Shing, Y. L., & Werkle-Bergner, M. (2019). Memory quality modulates the effect of aging on memory consolidation during sleep: Reduced maintenance but intact gain. *bioRxiv,* 547448. doi: 10.1101/547448.

**Paper IV**

**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,*1940. doi: 10.1038/s41598-018-36557-z.

## List of Abbreviations

| | |
|---|---|
| AASM | American Academy for Sleep Medicine |
| ACh | acetylcholine |
| EEG | electroencephalography |
| EMG | electromyography |
| EOG | electrooculography |
| (f)MRI | (functional) magnetic resonance imaging |
| (m)PFC | (medial) prefrontal cortex |
| MTL | medial temporal lobe |
| NREM | non-rapid eye movement |
| PLSC | Partial Least Squares Correlation |
| PSG | polysomnography |
| SWA | slow-wave activity |
| SWS | slow-wave sleep |
| VBM | voxel-based morphometry |
| REM | rapid eye movement |

## Glossary of Terms

**Acetylcholine (ACh):** Cholinergic neuromodulator and neurotransmitter with multiple functions including attention, memory, synaptic plasticity, and the regulation of sleep cycles

**Aging:** Process of change, taking place as organisms grow older

**Cognition:** Variety of mental operations related to information acquisition, storage, and usage (e.g., perception, attention, memory, problem solving, and decision making)

**Cognitive psychology:** Study of human cognition

**Cognitive neuroscience:** Study of the biological foundations of human cognition

**Cognitive neuroscience of aging:** Study of alterations in cognition and their biological foundations taking place as humans age

**Cortisol:** Main glucocorticoid in humans that is known for its reactivity to stress, and its metabolic and immunologic functions

**Cellular consolidation:** Initial and immediate local stabilization of new memory traces that relies on neurochemical changes on a synaptic level (also synaptic consolidation)

**Delta waves:** Homeostatically regulated low-frequency oscillations (< 4 Hz) characteristic for slow-wave sleep

**Downscaling:** Process during which the learning-induced increase in overall synaptic strength is down-regulated by slow-wave activity

**Electroencephalography (EEG):** Non-invasive technique measuring the postsynaptic potentials of neurons by placing electrodes on the scalp

**Entorhinal cortex:** Major input structure to the hippocampus in the medial temporal lobe and critical hub for the information flow between the hippocampus and neocortex

**Episodic memory:** Ability to consciously recollect specific episodes from the past together with their spatial and temporal context

**Fast spindles:** Spindle type (ca. 12.5–16 Hz) generated within thalamo-cortical feedback loops that is predominant over centroparietal brain areas

**Functional magnetic resonance imaging (fMRI):** Non-invasive technique measuring functional brain activity by the identification of changes in blood flow and oxygenation (cf. Magnetic resonance imaging)

**Hippocampus:** Structure in the medial temporal lobe that plays a key role in learning, spatial navigation, and long-term memory

**Homeostatic sleep pressure:** Sleep drive that is contingent on the duration of previous wakefulness

**Lifespan psychology:** Study of individual developmental change from conception to death

**Long-term memory:** Lasting storage of information over longer time periods (in contrast to short-term memory, that only lasts for a few seconds)

**Memory consolidation:** Process through which initially labile memories are stabilized, transformed, and integrated into existing knowledge networks to make them permanently accessible

**Magnetic resonance imaging (MRI):** Non-invasive technique creating detailed images of the brain (or other organs and tissues) by the use of strong magnetic fields

**Neurochemicals:** Umbrella term for (endogenous) chemical agents that act on the physiology of the nervous system (e.g., hormones, neurotransmitters, neuromodulators)

**Neuromodulation:** Physiological process that modulates neural properties and the efficacy of synaptic transmission by the release of chemical agents called neuromodulators (e.g., acetylcholine, dopamine, serotonin, norepinephrine)

**Non-rapid eye movement (NREM) sleep:** Sleep state that is marked by synchronous, low-frequency, high-amplitude oscillations

**Polysomnography (PSG):** Combined recordings of electroencephalography, eye movements, and muscle tone in order to assess and/or monitor an individual's sleep

**Rapid eye movement (REM) sleep:** Sleep state that is marked by the occurrence of phasic irregular and rapid eye movements, muscle atony, and desynchronized wake-like electroencephalographic activity

**Sharp-wave ripples:** Short discharges of large hippocampal neural assemblies superimposed by high-frequency (100–300 Hz) oscillations

**Sleep:** recurring natural state of reduced responsiveness to the environment and altered consciousness; defined by specific behavioral indicators (e.g., closed eyes or a recumbent body position) and physiological criteria (e.g., low muscle tone, slow heart rate, changes in neuromodulation and brain activity)

**Sleep spindles:** Waxing and waning oscillations with a frequency of 11–16 Hz and a duration of at least 0.5 seconds that are characteristic for stage 2 sleep

**Slow spindles:** Spindle type (ca. 9–12.5 Hz) that is predominant over frontal brain areas

**Slow oscillations:** Neocortical high-amplitude low-frequency oscillations (0.5–1 Hz) occurring throughout non-rapid eye movement sleep

**Slow-wave activity (SWA):** Neural activity within the slow oscillation and delta frequency range (0.5–4.5 Hz) that is most prevalent during slow-wave sleep

**Slow-wave sleep (SWS):** Sleep phase comprising non-rapid eye movement sleep stage 3 and 4 that is defined by the prevalence of slow-wave activity; sometimes referred to as deep sleep

**System consolidation:** Active consolidation process describing the reorganization of repeatedly reactivated recent memories between brain systems that results in a greater dependency of remote memories on long-term storage sites in the neocortex

**Thalamus:** Structure within the diencephalon that is known for its role in relaying sensory input and regulating sleep and consciousness

# Contents

*"Memory combines the countless individual phenomena of our consciousness into one whole,*
*and like our body would fall apart into countless atoms,*
*if the attraction of matter did not hold it together,*
*without the binding power of memory*
*our consciousness would fall apart into as many pieces as moments there are."*
— Hering, 1876, p. 12[1]

# 1 Introduction

Our remarkable ability to acquire new information, to form internalized knowledge networks of the surrounding world, and to permanently update existing knowledge networks is one of the most basic fundamentals that characterize us as conscious human beings. Memories of past experiences enable us to orient ourselves in the present with its complex environment, and to guide and adapt our actions dynamically by taking into account predictions about the future. Losing the ability to retain these essential memories will affect who we were, are, and will be.

Our capability to re-experience specific events or episodes together with their spatial and temporal context, is called *episodic memory* (Squire & Zola, 1996; Squire, 2004; Tulving, 1972, 1985, 1995). Episodic memories are part of our declarative (explicit) memory system that comprises the ability to consciously recollect specific memory contents like facts and events (Squire, 2004; Tulving, 1972). As long-term memories, these memory contents need to be retained over longer time scales – up to years and decades (Duszkiewicz, McNamara, Takeuchi, & Genzel, 2019; Redondo & Morris, 2011; Takeuchi, Duszkiewicz, & Morris, 2014). Therefore, memories require *consolidation* during which they are stabilized and strengthened, transformed, and integrated into existing knowledge networks (Dudai, Karni, & Born, 2015; Tonegawa, Pignatelli, Roy, & Ryan, 2015). Sleep shields our brain from external sensory input, minimizes cognitive interference (Hobson & Pace-Schott, 2002), and thereby offers optimal conditions for these global consolidation processes (Axmacher, Draguhn, Elger, & Fell, 2009; Diekelmann & Born, 2010; Mednick, Cai, Shuman, Anagnostaras, & Wixted, 2011).

[1] Original quote: *"Das Gedächtniß verbindet die zahllosen Einzelphänomene unseres Bewußtseins zu einem Ganzen, und wie unser Leib in unzählige Atome zerstieben müßte, wenn nicht die Attraction der Materie ihn zusammen hielte, so zerfiele ohne die bindende Macht des Gedächtnisses unser Bewußtsein in so viele Splitter, als es Augenblicke zählt."*

When sleep is insufficient, in the first place, key components of cognition are affected. Typically observed symptoms include impaired attention and long-term memory (Lowe, Safati, & Hall, 2017) – a pattern akin to cognitive changes observed during aging (Buckner, 2004; Craik, 2006; Lindenberger, 2014). Alterations in sleep physiology during aging may cause these cognitive alterations, impact memory consolidation, and thereby explain reduced memory performance in healthy aged individuals (Harand et al., 2012; Mander, Winer, & Walker, 2017; Scullin & Bliwise, 2015). However, sleep, memory, and aging are each highly complex research areas. Studying their interrelations is challenging and currently available evidence inconclusive.

Within this dissertation I aim to address the striking parallelism of age-related changes in sleep and memory. I will start this endeavour by emphasizing the lifelong dynamic nature of the human brain and cognition that provides a unique potential to understand the neural correlates of cognitive functions – yet, at the same time, complicates the scientific process tremendously. Based on this theoretical basis, I will investigate the neural machinery that drives the association between sleep and episodic memory consolidation in the aging brain. I intend to highlight – and possibly resolve – some of the key challenges in research linking sleep and memory in older adults. Finally, I will ask the fundamental and provoking question, why it is nevertheless worthwhile, or even inevitable, to face these challenge and study cognitive and cerebral aging.

# 2 Theoretical and Empirical Foundations

## 2.1 An Aging Perspective on Cognitive Neuroscience: Theoretical Foundations

*"Ontogenetic development is a lifelong process.*
*No age period holds supremacy in regulating the nature of development."*
— Baltes, 1987, p. 613

### 2.1.1 Lifespan Dynamics of Brain and Cognition

*Cognitive psychology* strives to decipher human cognition with its diverse mental operations that include perception, attention, memory, problem solving, and decision making (Anderson, 2013; Eysenck & Keane, 2013). To do so, research is making use of a wide range of theoretical models and empirical methods to integrate evidence across different levels of analysis. *Cognitive neuroscience*, thereby, is concerned with the biological bases of human cognition that can be found in the brain's structure, function, and neurochemistry (e.g., Gazzaniga, 2009). To investigate this, research has mostly relied on small and homogenous samples of highly educated, young, and healthy individuals whose neural prerequisites are presumed to be representative, optimal, and stable (Button et al., 2013; Henrich, Heine, & Norenzayan, 2010; Martz et al., 2013; Sears, 2008).

Yet, the brain is not as stable as it is often assumed. It acts as an inner neural machine that is embedded in its own organism and the outer environment, which permanently and dynamically interact with and shape each other (Baltes, Reuter-Lorenz, & Rösler, 2006; Clark, 1998; Li, 2003; Lindenberger, Li, & Bäckman, 2006; Martz et al., 2013). This allows personalized and adaptive cognition and behavior to emerge. In addition to this momentary between-level interaction, the brain is situated within its own life course. It is driven by personal antecedents and provokes specific repercussions that will, themselves, feed forward to its future status (e.g., Baltes, Reese, & Virginia, 1980; Baltes, 1987; Baltes, Reese, & Nesselroade, 1988; Baltes, Staudinger, & Lindenberger, 1998, 1999; Li, 2003; Lindenberger et al., 2006). The brain and its cognitive functions are continuously and systematically changing and adapting. Hence, evident inter-individual differences in studied phenomena must be regarded as results and at the same time as constituents of lifelong dynamic processes (Baltes et al., 1988; Lindenberger et al., 2006).

The inherently dynamic and constantly changing nature of brain and cognition can be placed within the field of *lifespan psychology* that emphasizes that cognitive development is a lifelong process (Baltes et al., 1980; Baltes, 1987; Baltes et al., 1998, 1999; Brandtstädter & Lindenberger, 2007; Craik, 2006). During the life course, individuals are confronted with phases of growth, maintenance, and decline (Baltes, 1987; Baltes et al., 1998; Brandtstädter & Lindenberger, 2007). These processes are continually active, but one may prevail over the others in certain developmental periods. Whereas structural and functional gains dominate most domains during maturation, losses may overshadow senescence (e.g., Fjell et al., 2013; Li et al., 2004; Ziegler et al., 2012). Crucially, young adulthood should not be regarded as the zenith and reversal point of development (Baltes, 1987; Baltes et al., 1998; Craik, 2006). Rather, it constitutes a phase marked by relative stability and constancy that may be maintained in case of 'successful' aging (Baltes et al., 1980; Baltes, 1987; Cabeza et al., 2018; Lindenberger et al., 2006; Nyberg, Lövdén, Riklund, Lindenberger, & Bäckman, 2012; Schulz & Heckhausen, 1996).

To conclude, as much as the brain and cognition are linked with each other and to the environment at a given moment in time, as much is this moment conditioned by an individual's overall life course. Within individuals, brain, cognition, and the mapping of both are constantly changing and adapting (Craik, 2006; Lindenberger et al., 2006). Recently, more and more studies have acknowledged that there is no such thing as a 'representative brain' or a 'representative state' in cognitive neuroscience (Gordon et al., 2017; Grandy, Lindenberger, & Werkle-Bergner, 2017; Laumann et al., 2015; Martz et al., 2013; Molenaar, 2004; Poldrack et al., 2015). The rich, dynamic, and variable nature of the brain warrants cognitive neuroscience to adopt a more comprehensive view on the human brain and cognition.

### 2.1.2 Cognitive Neuroscience of Aging

In light of the increasing longevity and global aging of the human population (Vaupel, 1998; Vaupel et al., 1998), research has never been more eager to identify the predictors and modifiers of healthy and 'successful' aging (Cabeza et al., 2018; Depp, Harmell, & Vahia, Ipsit, 2012; Nyberg et al., 2012; Nyberg & Pudas, 2018; Rowe & Kahn, 1987, 2015). One of the key components that constitutes successful aging is the maintenance of cognitive abilities (e.g.,

Cabeza et al., 2018; Depp et al., 2012; Nyberg & Pudas, 2018; Schulz & Heckhausen, 1996). Substantial inter-individual differences in the rate and timing of age-associated cognitive losses (Cabeza et al., 2018; Habib & Nyberg, 2007; Lindenberger, 2014; Lindenberger & von Oertzen, 2006) pose the question how the brain may preserve cognitive functioning in old age. By linking evidence on cognitive aging with research on age-associated alterations in brain anatomy, physiology, and functionality, the *cognitive neuroscience of aging* is searching for the neural mechanisms that drive the diverse and heterogeneous behavioral outcomes (Cabeza, 2001; Cabeza, Nyberg, & Park, 2005; Grady, 2012).

Until the early 90s, the cognitive neurosciences primarily viewed aging as a deficient process with progressive and irreversible declines in cognition and its neural foundations. To study how changes in cognition with advancing age correspond to changes in the central nervous system, research aimed to identify neurological patients whose cognitive deficits matched those of healthy older adults (Moscovitch & Winocur, 1995; West, 1996). By necessity, these lesion models of aging consider aging as a detrimental process. Rapid technological developments in non-invasive neuroimaging techniques, however, made it possible to study healthy populations. In this way, a more complete and thorough picture of the aging brain, cognition, and their interrelation can be drawn (Craik, 2006; National Research Council, 2000; Reuter-Lorenz, 2002). Although cognitive aging, in general (and not only in the presence of pathology), constitutes a period of decline, the aging pattern is far more complex, with overall great inter-individual differences in cognitive aging (Cabeza et al., 2018; Lindenberger & von Oertzen, 2006; Lindenberger, 2014) and functions such as semantic knowledge or implicit memory being largely preserved (Baltes, 1987; Craik & Bialystok, 2006; Li et al., 2004; Nilsson, 2003; Park, Polk, Mikels, Taylor, & Marshuetz, 2001; Park & Reuter-Lorenz, 2009). Moreover, brain function and brain–behavior mappings may differ both quantitatively and qualitatively across the lifespan (Cabeza, 2002; Cabeza et al., 2018; Craik, 2006; Grady, 2008, 2012; Park & Reuter-Lorenz, 2009; Reuter-Lorenz, 2002). Despite great scientific advances, undisputedly, more research is required to define the diverse behavioral and neural mechanisms that drive the complex changes in cognition during aging (National Research Council, 2000).

### 2.1.3 Studying Cognitive and Neural Aging: Boon and Bane

> *"The life-span integration of perspectives and findings, in turn,*
> *is hoped to feed back into more age- and process-specific developmental specialities,*
> *providing for larger integrative frameworks*
> *and provoking the investigation of new or formerly neglected research questions"*
> — Baltes et al., 1998, p. 596

When studying cognitive and neural aging, research encounters the complex and variable nature of neural processes under examination, and faces the appendant theoretical, methodological, and practical difficulties. At the same time, the complexity and malleability of the coupling between brain and cognition provide an enormous potential to understand the neurobiological underpinnings of cognitive processes (Grady, 2008; Lindenberger et al., 2006). Below, these potentials and pitfalls will be delineated and the scientific costs and gains accompanying the cognitive neuroscience of aging will be evaluated.

#### Potentials of the Cognitive Neuroscience of Aging

When delineating the promise the cognitive neuroscience of aging holds, we can take two perspectives: First, we can acknowledge the potential arising from a neuroscientific view on cognitive aging. Second, we can endorse the benefits the discipline of cognitive neuroscience gains when an aging perspective is included. Unfortunately, the second perspective has received little attention within the scientific literature, so far.

First and foremost, studying cognitive aging and its neural underpinnings forms the basis for the identification of predictors and modifiers of healthy and 'successful' aging (Cabeza et al., 2005, 2018; Depp et al., 2012; Grady, 2012; Nyberg et al., 2012; Nyberg & Pudas, 2018; Rowe & Kahn, 1987, 2015). Adding the layer of neuroscience is not just valuable but actually inevitable to gather a true mechanistic understanding of cognitive aging in its entirety. This forms the basis to define treatment targets for therapeutic interventions that may impede, delay, or even reverse (non-)pathological cognitive decline in aging (e.g., Hertzog, Kramer, Wilson, & Lindenberger, 2008; Karbach & Verhaeghen, 2014; Mander, Winer, Jagust, & Walker, 2016; Schmiedek, Lövdén, & Lindenberger, 2010; Wilckens, Ferrarelli, Walker, & Buysse, 2018).

Second, beyond its undeniable therapeutic potential, the cognitive neuroscience of aging provides scientists with a unique opportunity to question, and refine theoretical and

methodological conventions. In a nutshell, studying older adults' cognition can serve as a 'proof of concept' both in scientific theory and methodology. It can inform the researcher on possible limitations and confounds in theoretical frameworks, study designs or analytic procedures (see *Paper II* for more details). When studying high-functioning younger adults, one can easily neglect the importance of certain experimental conditions or variables. For instance, when investigating associative memory in healthy younger adults, one might overlook that the success of memory encoding is determined by the use of adequate memory encoding strategies, as younger adults, in contrast to older adults, automatically apply these strategies (Cohn, Emrich, & Moscovitch, 2008; Naveh-Benjamin, 2000; Naveh-Benjamin, Brav, & Levy, 2007; Shing, Werkle-Bergner, Li, & Lindenberger, 2008). Only by moving away from the 'optimal' participant and allowing for more variation in our empirical work, we are able to conceive and investigate a cognitive process and its neural correlates in their entirety (Gordon et al., 2017; Laumann et al., 2015; Martz et al., 2013; Nielsen, Haun, Kärtner, & Legare, 2017; Poldrack et al., 2015).

By including different age groups, inter-individual variation in study samples can be increased, statistical power can be boosted, and the dynamic nature of brain, cognition, and their mappings can be targeted (Browning & Spilich, 1981; Button et al., 2013; Lindenberger et al., 2006). In general, science has proven that complex systems can hardly be studied while they are constant or stable, but are better understood during their (re)organization (Deco, Jirsa, & McIntosh, 2011; Deco & Jirsa, 2012; McIntosh et al., 2010). Hence, cognitive neuroscience can profit from taking a lifespan perspective and including age periods that are known for cognitive and neural development and change (Lindenberger et al., 2006). This, in turn, can give rise to larger and more universal integrative theoretical frameworks (Baltes et al., 1998; Muthukrishna & Henrich, 2019; Overton, 2010).

**Intricacies in Studying the Aging Brain and Cognition**

Yet, studying the interplay of senescent changes in brain and cognition is clearly challenging. Beyond very practical difficulties like the recruitment of older participants or the application of neuroimaging techniques in samples of aged individuals' (e.g., Browning & Spilich, 1981; Samanez-Larkin & D'Esposito, 2008), research is immensely compounded by the complexity

of aging itself. Aging entails a variety of physiological, neural, and behavioral changes (e.g., Craik & Bialystok, 2006; Fjell & Walhovd, 2010; Grady, 2012; Li & Schmiedek, 2002) that will affect our way of theorizing and designing studies, collecting, processing, analyzing, and interpreting the data (Raz & Lindenberger, 2011; Rugg & Morcom, 2005; Samanez-Larkin & D'Esposito, 2008).

The multitude of variables and processes that change as humans age, poses the challenge to identify, measure, and control for confounding 'irrelevant' age differences (Browning & Spilich, 1981; Hertzog & Nesselroade, 2003). For instance, observed age differences in episodic memory encoding could, at least in part, be attributed to reduced attentional and processing resources (Anderson, Bjork, & Bjork, 2000; Buckner, 2004; Craik, Luo, & Sakuta, 2010; Craik & Rose, 2012). Age-comparative research, thus, needs to thoroughly control and adjust task designs, instructions, and analyses to offer precise and meaningful behavioral and neural indicators (Baltes et al., 1999; National Research Council, 2000; Naveh-Benjamin et al., 2007; Nesselroade, Gerstorf, Hardy, & Ram, 2007; Nesselroade & Molenaar, 2016).

Our insights into brain–cognition links are determined by the capacity of study designs, measurement instruments, and analysis techniques to meet the complex and multifaceted nature of aging (Dennis & Cabeza, 2001; Hedden & Gabrieli, 2004; Nesselroade & Molenaar, 2016; Raz & Nagel, 2007). Measurement techniques and analytic pipelines can be biased when applied to older populations, and results may not be easy to compare between age groups (Park et al., 2001; Samanez-Larkin & D'Esposito, 2008; see *Paper II* for more details). Moreover, as many neural and cognitive changes happen in parallel during aging (Hedden & Gabrieli, 2004; Tucker-Drob, Brandmaier, & Lindenberger, 2019), concomitant alterations in brain and behavior may be over- or misinterpreted in terms of cause–consequence relations (Lindenberger, von Oertzen, Ghisletta, & Hertzog, 2011; Raz & Lindenberger, 2011). Studies with gold-standard longitudinal designs are scarce, although the prevailing cross-sectional evidence suffers from critical confounds (Hertzog & Nesselroade, 2003; Hofer & Sliwinski, 2001; Li & Schmiedek, 2002; Lindenberger & Pötter, 1998; Lindenberger et al., 2011; Overton, 2010; Raz & Lindenberger, 2011; Rönnlund, Nyberg, Bäckman, & Nilsson, 2005; Wohlwill, 1970).

All in all, taking an aging perspective in cognitive neuroscience can clearly be valuable. Doing so, we not only broaden our knowledge on specific neural and cognitive dynamics, but also learn to question our current scientific practices in a constructive way. Yet, at the same time, the complexity of aging challenges research tremendously. As I will illustrate below, even though the intricacies of aging research complicate the scientific process, *"facing these difficulties is worth the effort, as the scientific promise in studying the ontogeny of mind and brain is truly outstanding"* (Lindenberger et al., 2006, p. 714).

### 2.1.4 Cognitive Neuroscience of Aging: The Case of Memory Consolidation

To illustrate what such a 'scientific promise' could look like in practice, this dissertation focuses on *episodic long-term memory*, that is, our ability to form and consciously recall memory episodes in conjunction with their spatio-temporal context (Squire, 2004; Squire & Zola, 1996; Tulving, 1972, 1985, 1995). To date, the majority of research in the cognitive neuroscience of aging has focused on episodic memory and usually adopts it as the prime example of the field (e.g., Cabeza, 2001; Cabeza et al., 2005, 2018; Grady, 2008, 2012; Reuter-Lorenz & Park, 2010). As aging is typically accompanied by a drastic decline in episodic memory performance, a substantial body of behavioral evidence is available (e.g., Burke & Light, 1981; Craik & McDowd, 1987; Naveh-Benjamin, 2000; Nilsson, 2003; Rönnlund et al., 2005; Singer, Verhaeghen, Ghisletta, Lindenberger, & Baltes, 2003; Smith, Park, Earles, Shaw, & Whiting, 1998).

Research on age differences and commonalities in episodic memory performance and its neural underpinnings mostly focuses on the interaction of the medial temporal lobe (MTL) and prefrontal cortex (PFC) (Eichenbaum, 2000, 2017; Moscovitch, Cabeza, Winocur, & Nadel, 2016; O'Reilly & Norman, 2002; Preston & Eichenbaum, 2013; Simons & Spiers, 2003). Developmental alterations in these brain systems and the associated cognitive processes have frequently been linked to lifespan changes in memory function (e.g., Buckner, 2004; Craik & Bialystok, 2006; Pudas, Josefsson, Rieckmann, & Nyberg, 2017; Shing et al., 2010). Due to structural and functional losses in both PFC and MTL areas (Buckner, 2004; Cabeza et al., 2005; Fjell & Walhovd, 2010; Fjell et al., 2013; Raz et al., 2005), older adults may forfeit their ability to create distinct and cohesive memory representations, and to monitor, evaluate, adapt,

and access them (Burke & Light, 1981; Craik & McDowd, 1987; Craik & Bialystok, 2006; Danckert & Craik, 2013; Fandakova et al., 2018; Shing et al., 2008, 2010; Werkle-Bergner, Müller, Li, & Lindenberger, 2006). However, so far, evidence and theories on episodic memory and aging have almost exclusively concentrated on memory encoding and retrieval. Yet, as I will point out in this dissertation, newly formed memories have to be maintained and consolidated in order to be successfully retrieved (Anderson et al., 2000; Craik & Rose, 2012; Habib, Nyberg, & Tulving, 2003; Naveh-Benjamin et al., 2007; Shing et al., 2010). To allow for this to happen, likewise, an intact and functional hippocampal–prefrontal loop is essential (Eichenbaum, 2017; Genzel et al., 2017; Preston & Eichenbaum, 2013; Wang, Redondo, & Morris, 2010). There is an evident need to close our knowledge gap between aging theories on memory encoding and retrieval and consider the importance of post-encoding consolidation processes (Craik & Bialystok, 2006; Shing et al., 2010).

Crucially, the described knowledge gap in conventional aging theories does not signify a lack of research on the neural processes that strengthen and store memories in old age. Research on memory consolidation has recently extended its main focus on healthy younger adults to more heterogeneous populations, including older adults (Harand et al., 2012; Scullin & Bliwise, 2015, for reviews). However, so far, results are barely integrated into broader theories on memory and aging.

In contrast to research on memory encoding and retrieval in aging, research on consolidation still appears to be constrained by the existence of two largely independent research fields: one process-oriented research field that elucidates the mechanisms during sleep that guide the consolidation of episodic memories (e.g., Diekelmann & Born, 2010; Klinzing, Niethard, & Born, 2019; Rasch & Born, 2013), and another research field that attempts to understand cognitive aging in its entirety (e.g., Cabeza et al., 2005; Grady, 2012). Research on age-related changes in episodic memory consolidation during sleep can hence serve as an example (1) to show how our knowledge on brain–cognition mappings can be advanced by considering the period of aging and (2) to illustrate how our knowledge on age-related changes in cognition can profit from considering the process of memory consolidation.

## 2.2 An Aging Perspective in Practice: Episodic Memory Consolidation During Sleep

### 2.2.1 Memory Consolidation: Some Basics

Memories are dynamic and evolve over time. During encoding, external information and internal thoughts are translated into neural memory representations (Craik & Rose, 2012; Josselyn, Köhler, & Frankland, 2015; Semon, 1904; Tonegawa et al., 2015). To transform these initially labile memory representations into lasting memories that are accessible during later retrieval, they require *consolidation*, that is, they are gradually strengthened and integrated into preexisting knowledge networks (Dudai et al., 2015; Duszkiewicz et al., 2019; Redondo & Morris, 2011; Takeuchi et al., 2014; Tonegawa et al., 2015). New memory traces are created and stabilized by neurochemical alterations on a cellular level that strengthen synaptic connections (Bliss & Lømo, 1973; Dudai, 2004; Mednick et al., 2011). This initial and instantaneous local *cellular consolidation* is supplemented by global *system consolidation*. The latter allows for a more flexible and adaptive transformation and strengthening of reactivated memory traces by reorganizing the memory's reliance on brain circuits or *systems* (Dudai, 2004; Frankland & Bontempi, 2005; Genzel et al., 2017). For episodic memories, a brain circuit linking MTL structures, in particular the *hippocampus*, with the temporal and frontal lobes is pivotal (Eichenbaum, 2000, 2017; McClelland, McNaughton, & O'Reilly, 1995; Moscovitch et al., 2016; Simons & Spiers, 2003). Hippocampal–prefrontal interactions are considered pivotal for monitoring and controlling encoding and retrieval operations (in a strategic top-down manner), and for building, updating, and assessing neocortical knowledge networks (i.e., schemata; for more details see Eichenbaum, 2000, 2017; Miller & Cohen, 2001; O'Reilly & Norman, 2002; Preston & Eichenbaum, 2013; Simons & Spiers, 2003). Whereas the hippocampus may serve as temporary memory store, that binds new information into a transient representation, neocortical brain regions may constitute the brain's long-term storage sites (Frankland & Bontempi, 2005; McClelland et al., 1995).

### 2.2.2 Sleep-Associated Memory Consolidation in Younger Adults

#### Brief Historical Outline: From Behavioral Studies to Cognitive Neuroscience

> *"We know little about what happens in the nervous system when one forgets.* [...]
> *It is more fruitful to work out our explanations at the level of experimental fact.*
> *When these facts are, some day, given their place in the neurophysiology and biochemistry*
> *of the organism, they will have been placed in a wider perspective,*
> *but it is doubtful if their specific significance will have been greatly altered."*
> — McGeoch, 1932, p. 368

In his series of experiments, Ebbinghaus (1885) was probably the first to experimentally demonstrate that forgetting is a function of time, that is attenuated over intervals that include sleep. Between 1892 and 1900, Müller and Pilzecker continued this series of experiments and introduced the term 'Konsolidierung' (Müller & Pilzecker, 1900), covering a set of post-learning physiological processes necessary to strengthen the associations of learned syllables (Lechner, Squire, & Byrne, 1999). Within the next 30 years, first systematic approaches were taken to study the beneficial effect of sleep on memory retention (e.g., Heine, 1914; Jenkins & Dallenbach, 1924; see van Ormer, 1933, for an early review). By varying the time of encoding and retrieval and the length of the retention interval, two main assumptions emerged: Forgetting was believed to arise from a time-dependent decay of memory traces (Thorndike, 1914) and from retroactive interference of new learning material overwriting old memories (Jenkins & Dallenbach, 1924; Lechner et al., 1999). The initially proposed passive protective role of sleep, though, was soon challenged (McGeoch, 1932; Ellenbogen, Payne, & Stickgold, 2006, for a more recent review). It was postulated that *"time, in and of itself, does nothing"*, and that *"disuse is important only in that it so often gives the primary conditions an opportunity to act"* (McGeoch, 1932, p. 359). In 1933, in the first literature review of the relation between sleep and memory retention, van Ormer summarized the scientific evidence as follows: *"In conclusion, suffice it to say that the whole problem is a complex one. The statement that the rate of forgetting diminishes with time is hardly correct as an unqualified statement; and the explanation that forgetting is produced by the physiological law of atrophy through disuse is far from complete"* (van Ormer, 1933, p. 473).

Since the 1920s it became possible to measure the brain's electric fields non-invasively, more precisely the postsynaptic potentials of neurons, by the use of scalp electroencephalography

(EEG; Berger, 1929; Biasiucci, Franceschiello, & Murray, 2019). Combined recordings of EEG, eye movements (electrooculography [EOG]), and muscle tone (electromyography [EMG]), so-called *polysomnography* (PSG) , are nowadays standard methods for objective sleep assessments (see Iber, Ancoli-Israel, Chesson, & Quan, 2007; Rechtschaffen & Kales, 1968). Based on these recordings, it was early on acknowledged that sleep does not only represent a distinct behavioral, but also a distinct physiological state that is characterized by the cyclic alteration of two discrete sleep types: *rapid eye movement* (REM) and *non-REM* (NREM) sleep (Aserinsky & Kleitman, 1953; Dement & Wolpert, 1958; Feinberg & Evarts, 1969; Loomis, Harvey, & Hobart, 1935, 1962). Whereas REM sleep is marked by the occurrence of phasic irregular and rapid eye movements, muscle atony, and desynchronized wake-like electroencephalographic activity, NREM sleep is characterized by synchronous, low-frequency, high-amplitude EEG oscillations (Hobson & Pace-Schott, 2002; Iber et al., 2007; see *Paper II*, for more details on the electrophysiology of sleep). It was only after the discovery of these distinct physiological sleep states (Aserinsky & Kleitman, 1953), that research on the active role of sleep in the consolidation of memories gained pace (Ellenbogen et al., 2006).

After an initial focus on REM sleep (Empson & Clarke, 1970; Lewin & Glaubmann, 1975), NREM sleep and its fundamental role for consolidating declarative memories were soon acknowledged (Barrett & Ekstrand, 1972; Fowler, Sullivan, & Ekstrand, 1972; Yaroush, Sullivan, & Ekstrand, 1971). Early approaches of (partial) sleep deprivation (Lewin & Glaubmann, 1975) were advanced by the pivotal work by Ekstrand and colleagues (Barrett & Ekstrand, 1972; Fowler et al., 1972; Yaroush et al., 1971) who elegantly made use of the homeostatic regulation of sleep. *Slow-wave activity* (SWA), that is rhyhtmic neural activity within the slow oscillation and delta frequency range (i.e., 0.5–4.5 Hz) and the defining criterion of deep NREM sleep (so-called *slow-wave sleep* [SWS]), constitutes an established marker of homeostatic sleep pressure (Achermann & Borbély, 1999; Vyazovskiy et al., 2009). It is at its maximum at the beginning of the night but attenuates thereafter (Achermann & Borbély, 1999; Bersagliere & Achermann, 2010). REM sleep, in contrast, prevails during the second half of the night. Varying the time of learning and recall between the first and second half of the night, it was possible to compare SWS-rich and REM-sleep-rich periods. This revealed the differential involvement of distinct physiological states during sleep in the consolidation of declarative and

procedural memory contents (Backhaus et al., 2007; Barrett & Ekstrand, 1972; Fowler et al., 1972; Plihal & Born, 1997; Yaroush et al., 1971). Whereas REM sleep was believed to support the consolidation of procedural memories, SWS and NREM sleep were linked to declarative memory consolidation (Ackermann & Rasch, 2014; Rauchs, Desgranges, Foret, & Eustache, 2005; Smith, 2001, for reviews). Other lines of experiments examined post-learning changes in sleep (Smith & Lapp, 1991; Verschoor & Holdstock, 1984), and the effect of presenting non-awakening memory cues during specific sleep stages on memory retention (e.g., Rasch, Büchel, Gais, & Born, 2007; Schouten, Pereira, Tops, & Louzada, 2017, for an overview). Still, it took until the early 2000s with the seminal advances in human neuroimaging, for a more mechanistic understanding of memory consolidation in humans to be gained (e.g., Maquet et al., 2000; Peigneux et al., 2003, 2004; Takashima et al., 2006). *"In the end, the question appears not to be whether sleep mediates learning and memory consolidation, but instead, how it does so"* (Walker & Stickgold, 2004, p. 131).

**The Active System Consolidation Account**

The prevailing theoretical framework guiding research on memory consolidation today is the *active system consolidation account* (e.g., Born & Wilhelm, 2012; Diekelmann & Born, 2010; Klinzing et al., 2019; Rasch & Born, 2013; see *Paper I* Figure 2A for a schematic). It is based on two main observations: Memories are *reactivated* during sleep and *redistributed* among brain systems (Ji & Wilson, 2007; Kudrimoti, Barnes, & McNaughton, 1999; McClelland et al., 1995; Scoville & Milner, 1957; Wilson & McNaughton, 1994). Episodic memories are initially processed both in the neocortex and in the hippocampus. By rapidly integrating diverse features and binding them into coherent memory representations, the hippocampus plays a key role in the acquisition of episodic memories (Frankland & Bontempi, 2005; Preston & Eichenbaum, 2013; Simons & Spiers, 2003). The acquired hippocampal and neocortical memory contents are then repeatedly reinstated, which results in the gradual strengthening of memory representations in cortical areas (Frankland & Bontempi, 2005; McClelland et al., 1995). In the course of this 'transformation,' memory representations may be integrated into preexisting neocortical memory networks and eventually lose their initial dependency on the hippocampus (Kitamura et al., 2017; Scoville & Milner, 1957; Sekeres, Moscovitch, & Winocur, 2017; Takashima

et al., 2009, 2006). These two processes (i.e., the reactivation and redistribution of memory representations) form the basis for an active transformation of memories and primarily take place during NREM sleep (for reviews, e.g., Born & Wilhelm, 2012; Diekelmann & Born, 2010; Inostroza & Born, 2013; Klinzing et al., 2019; Mednick et al., 2011; Rasch & Born, 2013; see *Paper I* for more details). The described 'push-action' of potentiating relevant memory traces, is believed to be complemented by a 'pull-action' that is driven by slow delta waves (< 4 Hz; Achermann & Borbély, 1999; Amzica & Steriade, 1998; Steriade, Nunez, & Amzica, 1993; Steriade, 2003). They promote a homeostatic synaptic *downscaling* by which redundant memory traces are erased (Cirelli, 2017; De Vivo et al., 2017; Genzel et al., 2017; Nere, Hashmi, Cirelli, & Tononi, 2013; Tononi & Cirelli, 2006, 2014, 2016, for details).

The timed release of specific neurochemicals during NREM sleep facilitates the transformation of labile hippocampus-dependent memory representations into lasting neocortical representations (Feld & Born, 2019). In particular, the cholinergic (i.e., acetylcholine [ACh]) and glucocorticoid systems (i.e., cortisol) regulate the information flow between the hippocampus and neocortex and allow for the fine-tuned succession of specific rhythmic neural activity patterns during NREM sleep (Axmacher & Rasch, 2017; Diekelmann & Born, 2010; Hasselmo, 1999; Micheau & Marighetto, 2011; Power, 2004; Rasch & Born, 2013; Wagner & Born, 2008). High-amplitude, low-frequency *slow oscillations* (0.5–1 Hz), the hallmarks of deep NREM sleep, globally synchronize neural activity in the brain. Slow oscillations are generated within cortical networks and reflect alternating down-states of prolonged neuronal hyperpolarization and up-states of depolarization. In particular, they enable hippocampal–neocortical memory processing by precisely timing hippocampal memory reactivations during periods of maximized neocortical synaptic plasticity (Crunelli et al., 2018; Maingret, Girardeau, Todorova, Goutierre, & Zugaro, 2016; Rasch & Born, 2013; Sirota, Csicsvari, Buhl, & Buzsáki, 2003; Staresina et al., 2015; Steriade, 1999, 2003, 2006). To do so, they orchestrate the occurrence of high-frequency oscillations (100–300 Hz) within the hippocampus, known as *sharp-wave ripples*, with *sleep spindles* (Axmacher, Elger, & Fell, 2008; Crunelli et al., 2018; Girardeau & Zugaro, 2011; Peyrache, Khamassi, Benchenane, Wiener, & Battaglia, 2009; Siapas & Wilson, 1998; Steriade, 1999, 2003). These *fast spindles*, distinct and brief oscillatory events with a typical frequency of 12.5–16 Hz (Contreras &

Steriade, 1996; Steriade, Domich, Oakson, & Deschenes, 1987; Steriade, 2003), are generated within thalamo-cortical feedback loops. They synchronize cortical activity in a precise spatio-temporal manner (Muller et al., 2016; Schabus et al., 2007; Siapas & Wilson, 1998) and may facilitate synaptic plasticity in hippocampal and neocortical brain regions by inducing a massive influx of $Ca^{2+}$ into excited neurons (Crunelli et al., 2018; Steriade, 1999). A second slower spindle type (ca. 9–12.5 Hz), which is dominant over frontal brain regions, is coupled to the transition of depolarized slow oscillation up-states and hyperpolarized down-states (Ayoub et al., 2013; Klinzing et al., 2016; Schabus et al., 2007; Timofeev & Chauvette, 2013). These *slow spindles* have been suggested to mirror cortico-cortical communication (Doran, 2003), but their exact role in memory consolidation remains to be revealed (Barakat et al., 2011; Mölle, Bergmann, Marshall, & Born, 2011).

To conclude, nowadays, memory consolidation is mainly viewed as an active process during which initially labile hippocampus-dependent memory representations are transformed into stable neocortical representations. It is assumed, that this active system consolidation is facilitated by precisely orchestrated neural activity patterns during NREM sleep that guide and time the reactivation, transformation, and stabilization of memories. As I will discuss next, in the last two decades research unravelling the proposed framework has flourished – and so did our knowledge on the mechanisms that guide the consolidation of episodic memories during sleep increment.

## Current State of Research

*"Our understanding of how consolidation works*
*– and our awareness of how much we still do not know about it –*
*have both increased enormously."*
— Genzel & Wixted, 2017, p. 13

Until the beginning of the millennium, mechanistic views on memory consolidation were primarily based on animal experiments and early human lesion studies (Buzsáki, 1998; Hasselmo, 1999; McClelland et al., 1995, for reviews). These were then gradually integrated with more recent findings from non-invasive neuroscientific research in healthy younger adults (Gais & Born, 2004; Peigneux, Laureys, Delbeuck, & Maquet, 2001; Smith, 2001). In 2004, Gais and Born provided the first mechanistic depiction of the processes guiding memory

consolidation during sleep in healthy younger adults. They emphasized that *"it is far from being well-established that these mechanisms* [i.e., the mechanisms of the active system consolidation account described in the previous section] *play a causative role for declarative memory consolidation during sleep"* (Gais & Born, 2004, p. 684). Yet, the core concepts of the active system consolidation account have persisted as they appear to be compatible with the majority of published empirical work (see Klinzing et al., 2019; Rasch & Born, 2013, for more recent reviews).

The spontaneous reactivation of memory traces during offline periods is considered integral for the active consolidation of memories (Born, Rasch, & Gais, 2006; Deuker et al., 2013; Ji & Wilson, 2007; Rasch & Born, 2013; Schönauer et al., 2017; Wilson & McNaughton, 1994). In animal studies, a reactivation of neural spiking patterns during sleep similar to task-related neural firing sequences was found (Ji & Wilson, 2007; Wilson & McNaughton, 1993). In humans, the reactivation of memories during sleep can be externally targeted by presenting subjects with non-awakening sensory memory cues like odors or sounds (see Oudiette & Paller, 2013; Schouten et al., 2017, for reviews). Studies have consistently shown that re-exposing subjects to memory cues during NREM sleep (but not REM sleep) promotes post-sleep memory performance (e.g., Cordi, Diekelmann, Born, & Rasch, 2014; Oudiette & Paller, 2013; Rasch et al., 2007; Schouten et al., 2017). Lately, the availability of advanced multivariate tools to study EEG and functional magnetic resonance imaging (fMRI) data (e.g., multivariate pattern classification or representational similarity analysis; cf. Haynes & Rees, 2006; Kriegeskorte, Mur, & Bandettini, 2008; McIntosh & Mišić, 2013) has revealed that neural activity patterns specific to memory contents are indeed reactivated in response to memory cues during sleep (Cairney, Marj, & Staresina, 2018; Schreiner, Doeller, Jensen, Rasch, & Staudigl, 2018; Shanahan, Gjorgieva, Paller, Kahnt, & Gottfried, 2018; Wang et al., 2019).

The active system consolidation account assumes that the reactivation and transfer of memory contents is enabled by the precisely timed interplay of slow oscillations, spindles, and sharp-wave ripples (Diekelmann & Born, 2010; Klinzing et al., 2019; Rasch & Born, 2013). In humans, various studies have linked declarative memory consolidation to fast thalamo-cortical sleep spindles (Cox, Hofman, & Talamini, 2012; Genzel, Dresler, Wehrle, Grözinger, & Steiger, 2009; Holz et al., 2012; Piosczyk et al., 2013; Ruch et al., 2012; Saletin, Goldstein, & Walker,

2011; Schabus et al., 2004), and proportions of SWS and NREM sleep (Backhaus et al., 2006; Clemens, Fabó, & Halász, 2005; Lau, Tucker, & Fishbein, 2010; Takashima et al., 2006). In rats, spontaneous hippocampal memory replay is mainly observed during SWS (Ji & Wilson, 2007). The enhancement of low-frequency oscillatory activity during NREM sleep by auditory or transcranial electrical stimulation promotes the consolidation of episodic memories in younger adults (e.g., Marshall, Mölle, Hallschmid, & Born, 2004; Ngo, Martinetz, Born, & Mölle, 2013; for reviews and meta-analytic evidence: Barham, Enticott, Conduit, & Lum, 2016; Bellesi et al., 2014; Marshall & Campos-Beltrán, 2017; Wilckens, Ferrarelli, et al., 2018; Zhang & Gruber, 2019). By strengthening the coordinated pattern of slow oscillations, spindles, and sharp-wave ripples in rats, Maingret et al. (2016) showed that it is indeed the precise interplay of these oscillatory components that facilitates memory consolidation.

Despite the large body of evidence supporting the active system consolidation account, a variety of studies has failed to observe the proposed positive relationship between memory consolidation and sleep physiology (e.g., Ackermann, Hartmann, Papassotiropoulos, de Quervain, & Rasch, 2015; Lo, Dijk, & Groeger, 2014; Pardilla-Delgado & Payne, 2017; Payne et al., 2009; Piosczyk et al., 2013). In a seminal investigation by Ackermann and colleagues, no association between episodic memory consolidation and various NREM and REM sleep parameters was detected in a sample of 929 healthy younger adults (Ackermann et al., 2015). These results highlight that there there is a need to reconsider the way we investigate sleep-associated memory consolidation and adapt our research to the underlying theoretical frameworks (cf. Conte & Ficca, 2013; Mantua, 2018). In this regard, inter-individual differences in the mere occurrence of certain sleep markers might be insufficient to explain memory consolidation during sleep as successful consolidation relies on the fine-tuned interplay of multiple oscillatory components (Latchoumane, Ngo, Born, & Shin, 2017; Maingret et al., 2016; Marshall & Born, 2007).

All in all, the general view on the mechanisms guiding the consolidation of declarative memories during sleep has changed remarkably little in the last two decades (Axmacher & Rasch, 2017; Born et al., 2006; Diekelmann & Born, 2010; Klinzing et al., 2019; Marshall & Born, 2007; Rasch & Born, 2013; Walker, 2009). However, this does not imply that the field has not advanced. Frameworks and hypotheses have been updated and refined to integrate

current empirical evidence and novel findings (e.g., Duszkiewicz et al., 2019; Genzel et al., 2017 for the role of novelty and dopaminergic modulation). Seemingly opposing theoretical camps were unified to provide a more holistic view of memory consolidation during sleep (e.g., Dash, Hebert, & Runyan, 2004; Genzel et al., 2017; Klinzing et al., 2019; Mednick et al., 2011, for an integration of the cellular and system consolidation account). Nevertheless, as evident from the growing number of null findings in the field (e.g., Ackermann et al., 2015; Lo et al., 2014; Pardilla-Delgado & Payne, 2017; Payne et al., 2009; Piosczyk et al., 2013), the last two decades have also taught us that the gap between proposed theoretical frameworks and actual empirical evidence remains wider than expected. To resolve inconsistencies in the literature, advance the field, and enrich the active system consolidation account, optimized study designs and improved analytic tools and statistical methods are necessary.

### 2.2.3 Sleep-Associated Memory Consolidation in Healthy Aging

At the same time as research on memory consolidation in younger adults is trying to fill remaining knowledge gaps and overcome the aforementioned methodological difficulties, a new research field is steadily growing and blossoming: research on the link between sleep and memory in aging. In general, it is believed that the observed drastic decline in SWS during aging could constitute a potential pathway to explain episodic memory deficits in old age (e.g., Harand et al., 2012; Mander, Rao, Lu, Saletin, Lindquist, et al., 2013; Mander et al., 2017; Varga et al., 2016).

In a strict sense, research on the association between age-related changes in sleep and cognition is not new *per se* (e.g. Feinberg, Koresko, & Heller, 1967; Prinz, 1977). It was motivated by the observation of pronounced changes in sleep during aging that are paralleled by a strong decline in episodic memory performance (Burke & Light, 1981; Carskadon, Brown, & Dement, 1982; Craik & McDowd, 1987; Landolt, Dijk, Achermann, & Borbély, 1996; Lombardo et al., 1998; Mander et al., 2017; Naveh-Benjamin, 2000; Nilsson, 2003; Ohayon, Carskadon, Guilleminault, & Vitiello, 2004; Prinz, Vitiello, Raskind, & Thorpy, 1990; Rönnlund et al., 2005; Singer et al., 2003; Smith et al., 1998; Webb, 1982). With emergence of a clearer understanding of the mechanisms guiding memory consolidation in young age, though, research in older adults has become more systematic and manifold evidence has been

collected (e.g., Backhaus et al., 2007; Baran, Mantua, & Spencer, 2016; Helfrich, Mander, Jagust, Knight, & Walker, 2018; Mander, Rao, Lu, Saletin, Lindquist, et al., 2013; Scullin, 2012; Wilson, Baran, Pace-Schott, Ivry, & Spencer, 2012; Scullin & Bliwise, 2015, for a review; see *Paper I* for a detailed overview). Overall, most studies reveal that episodic memory consolidation during sleep is impaired in old age (e.g., Cherdieu, Reynaud, Uhlrich, Versace, & Mazza, 2014; Mander, Rao, Lu, Saletin, Lindquist, et al., 2013; Varga et al., 2016; Gui et al., 2017, for meta-analytic evidence). Nevertheless, it remains ambiguous which factors impact memory consolidation during aging, and how they do so (Scullin & Bliwise, 2015). A theoretical evaluation and integration of the existing empirical evidence is yet to be done.

It can be argued that the ever-growing research focus on memory consolidation in aging in the last decades has been motivated by three lines of reasoning:

First, research has been tempted by the possibility to test specific hypotheses in terms of 'quasi-experimental' studies. By comparing age groups that differ in a specific sleep process of interest that is prone to aging, causal mechanisms can possibly be revealed. For instance, older adults with reduced levels of SWS may constitute an appropriate 'model' to prove the causality of SWS for episodic memory consolidation (Hornung, Danker-Hopfe, & Heuser, 2005). However, this idea is challenged by the complexity of aging, with collinear and parallel changes in neural and cognitive processes that are not under experimental control (e.g., Craik & Rose, 2012; Garrido, De Blas, Giné, Santos, & Mora, 2012; Lupien et al., 1998; Lynch, Rex, & Gall, 2006; Naveh-Benjamin et al., 2007; Raz & Rodrigue, 2006; Tucker-Drob et al., 2019; Ziegler et al., 2012). Insufficient memory encoding, for example, a typical finding in older adults (Craik & Rose, 2012, for a review), may limit how well memories can be maintained (cf. Conte & Ficca, 2013). Accordingly, two studies have reported that high-performing older adults are not impaired in their ability to consolidate memories across a night's sleep (Sonni & Spencer, 2015; Wilson et al., 2012). To draw causal inferences on consolidation processes that are specific to sleep, aging research must acknowledge the multifactorial contingency of memory consolidation.

Second, research was, and is intrigued by the aim to explain, reduce, delay, or even reverse the pronounced loss in episodic memory performance in aging. Experimental studies manipulating SWA in older adults in order to counteract deficits in memory consolidation

have provided very inconsistent results, though (Eggert et al., 2013; Ladenbauer et al., 2016, 2017; Papalambros et al., 2017; Paßmann et al., 2016; Westerberg et al., 2015). Still, empirical evidence is often interpreted as proof of the therapeutic potential of sleep interventions in old age (e.g., Helfrich et al., 2018; Ladenbauer et al., 2016; Mander, Rao, Lu, Saletin, Ancoli-Israel, et al., 2013; Mander, Rao, Lu, Saletin, Lindquist, et al., 2013; Papalambros et al., 2017). Again, it is often disregarded that memory consolidation is facilitated by a complex machinery of various mechanisms that may all be prone to detrimental aging effects (but see Helfrich et al., 2018; Mander, Rao, Lu, Saletin, Lindquist, et al., 2013; Varga et al., 2016, for recent propositions how structural brain integrity relates to sleep physiology and memory consolidation in old age). Low-frequency oscillatory activity during deep NREM sleep may contribute to consolidation processes during sleep – it may even be the driving force (cf., Mander, Rao, Lu, Saletin, Lindquist, et al., 2013). Yet, the multifaceted nature of age-related alterations in brain anatomy, physiology, and functionality make a holistic consideration of the processes that jointly shape the course of age-specific memory impairments imperative.

Finally, the idea that sleep can account for age-related neurodegenerative pathologies has recently attracted much attention (Ju, Lucey, & Holtzman, 2014; Mander et al., 2016; Noble & Spires-Jones, 2019; Vaou, Lin, Branson, & Auerbach, 2018). Disrupted sleep is commonly one of the earliest symptoms of Alzheimer's disease (Lim, Kowgier, Yu, Buchman, & Bennett, 2013; Lucey et al., 2019). However, it may also intensify, accelerate, or even cause cognitive pathology in late adulthood (Shokri-Kojori et al., 2018; Vaou et al., 2018). In the last years, sleep deprivation and disrupted sleep have frequently been linked to an accumulation of amyloid-$\beta$ and tau aggregates, both typical brain deposits of Alzheimer's disease (e.g., Lucey et al., 2019; Mander et al., 2015; Shokri-Kojori et al., 2018; Winer et al., 2019). For instance, it has been suggested that disrupted NREM sleep in aging might promote the accumulation of amyloid-$\beta$ in cortical areas, which could impact memory consolidation in turn (Mander et al., 2015, 2016). Corresponding studies on clinical populations and longitudinal studies, however, are yet to be conducted.

Especially the last two points, the hope to explain and 'cure' non-pathological and pathological memory deficits in older adults, have lately sparked great public and scientific interest (Mander et al., 2016; Noble & Spires-Jones, 2019; Wilckens, Tudorascu, et al., 2018).

Although ever more research is being carried out, it appears that the methodological intricacies that already challenge research in younger adults are even augmented in studies with older adults (e.g., Webb, 1982; Webb & Dreblow, 1982; Wendt et al., 2012; see *Paper II* for details). Besides, only recently have studies started to provide a more cohesive view on aging that includes changes in brain structure and function, beyond alterations in sleep physiology and memory (Baran et al., 2016; Helfrich et al., 2018; Mander, Rao, Lu, Saletin, Lindquist, et al., 2013; Varga et al., 2016; see *Papers III* and *IV*). Taken together, research appears to be torn between the methodological challenges of studying cognitive and cerebral aging and the great scientific potential arising when unravelling the links among sleep, memory, and aging. If this balance is struck, research on cognitive aging will progress significantly and our general understanding of the processes guiding episodic memory consolidation during sleep will advance.

Research on sleep-associated memory consolidation in healthy old age is no longer in its infancy – yet, a mechanistic understanding of the processes that lead to an insufficient stabilization of declarative memories during sleep is lacking. This work builds upon previous evidence assuming that the drastic decline in deep NREM sleep plays a major role in observed age-related deficits in memory consolidation (e.g., Harand et al., 2012; Mander, Rao, Lu, Saletin, Lindquist, et al., 2013; Mander et al., 2017; Varga et al., 2016). On the basis of four publications, this dissertation broadens and complements the focus of previous research (reviewed in *Paper I*) by considering how the success of memory consolidation during sleep is contingent on (1) the quality of individual memories (Conte & Ficca, 2013; Fenn & Hambrick, 2013; Schreiner et al., 2018; Tulving, 1964, 1967; *Paper III*), (2) the synergy of slow oscillations and sleep spindles (Helfrich et al., 2018; *Paper IV*), (3) and the structural integrity of the brain (Helfrich et al., 2018; Mander, Rao, Lu, Saletin, Lindquist, et al., 2013; Varga et al., 2016; *Papers II*, *III*, and *IV*).

# 3 Aims of Dissertation

Given the addressed tightrope walk between intricacies and potentials of studying cognitive and cerebral aging that strongly influence research on sleep-associated episodic memory consolidation, my dissertation pursues the following objectives:

**Overall objective:** To refine the active system consolidation account and theories on memory aging by investigating the neural mechanisms that drive the association between sleep and episodic memory consolidation in the aging brain.

**Subgoal 1:** To assess the current state of empirical evidence on the link between episodic memory consolidation, sleep (as measured by PSG), and aging and to derive an explanatory framework of the mechanisms guiding age-related alterations in episodic memory consolidation during sleep (*Paper I*).

**Subgoal 2:** To advance methodological practices in research on sleep, memory, and aging.

a. *Sleep*. To determine key challenges in the analysis of sleep PSG data in samples of older adults (*Paper II*).
b. *Memory*. To demonstrate the importance of deploying age-adapted memory tasks with tightly controlled encoding conditions to derive meaningful and age-fair estimates of memory consolidation (*Papers III* and *IV*).
c. *Sleep and Memory*. To establish theoretical and methodological alternatives for testing sleep–memory associations that extend conventional bivariate sleep stage–memory correlation coefficients (*Papers III* and *IV*).
d. *Aging*. To acknowledge the complexity of aging that, beyond altering sleep physiology, globally affects structural properties of the brain (*Papers I*, *II*, *III*, and *IV*).

# 4 Overview of Papers

The present dissertation is based on four articles that provide a theoretical and empirical perspective on sleep-associated episodic memory consolidation in healthy aging. *Paper I* offers a theoretical view on sleep-associated episodic memory consolidation in the aging brain. It integrates the currently available literature on this topic and links it to the active system consolidation account. *Paper II* bridges theory and empiricism by exemplifying and discussing analytic intricacies in research on the interplay between sleep and aging. Finally, in *Paper III* and *IV*, we take an empirical approach. *Papers III* and *IV* build upon the first two papers and put their methodological considerations into practice to link the consolidation of episodic memories with indices of sleep physiology and brain structure in younger and older adults. *Papers II*, *III*, and *IV* make use of the same empirical data set, which is briefly introduced at the beginning of *Paper II*.

## 4.1 Paper I: Summary and Integration of Current Literature

**Muehlroth, B. E.**, Rasch, B., & Werkle-Bergner, M. (under review). *Episodic memory consolidation during sleep in healthy aging*.

In this review article, the *status quo* of research on the interrelations among sleep, episodic memory, and aging is summarized. On this basis, we derive a cohesive explanatory framework that describes how age-related changes in memory consolidation during sleep emerge.

### Summary of Contents

The literature review starts by defining *episodic memory* and *sleep* and summarizing their interrelation as described within the active system consolidation framework (cf. p. 14; e.g., Diekelmann & Born, 2010; Gais & Born, 2004; Rasch & Born, 2013). Memories are actively reactivated during sleep, transformed, and integrated into existing knowledge networks (Born et al., 2006; Diekelmann & Born, 2010; Marshall & Born, 2007). This cascade of sleep-related memory processing is enabled by certain oscillatory dynamics during NREM sleep and supported by a specific setup of neuromodulators (Hasselmo, 1999; Power, 2004; Steriade,

2003). Together, this enables the transformation of transient hippocampus-dependent memory contents into durable neocortical memory traces (Frankland & Bontempi, 2005; Kitamura et al., 2017).

In a next step, we highlight how both sleep and memory functions change with advancing age (e.g., Ohayon et al., 2004; Shing et al., 2010). In short, episodic memory performance declines in older adults (Nilsson, 2003; Rönnlund et al., 2005). Overall sleep architecture changes and NREM-specific oscillations (i.e., slow oscillations and spindles) occur less often, with reduced amplitude, and altered topography (Carrier et al., 2011; Crowley, Trinder, Kim, Carrington, & Colrain, 2002; Mander et al., 2017; Ohayon et al., 2004). Moreover, gray matter volume decreases, white matter degenerates, and levels of neurochemicals that critically contribute to the phenomenon of memory consolidation change (Bäckmann, Nyberg, Lindenberger, Li, & Farde, 2006; Buckner, 2004; Fjell & Walhovd, 2010; Lupien et al., 1998; Raz et al., 2005; Schliebs & Arendt, 2006; Ziegler et al., 2012; see *Paper I* Figure 1 for a schematic).

We then continue to review the currently available evidence on the links between episodic memory, sleep, and aging step-by-step. Starting from behavioral evidence on memory consolidation in old age, we proceed to its links to sleep physiology, brain structure, and function, as well as neurochemistry. We acknowledge that differential memory tasks and experimental procedures, varying age ranges, and small sample sizes make it difficult to amalgamate currently available evidence. Still, most studies emphasize that the consolidation of episodic memories during sleep is hampered during aging (e.g., Cherdieu et al., 2014; Mander, Rao, Lu, Saletin, Lindquist, et al., 2013; Varga et al., 2016; Gui et al., 2017, for meta-analytic evidence). In particular, the decline in SWA during aging may be associated with impaired episodic memory consolidation (Backhaus et al., 2007; Mander et al., 2015; Mander, Rao, Lu, Saletin, Lindquist, et al., 2013; Papalambros et al., 2017; Varga et al., 2016; Westerberg et al., 2012, 2015). However, both correlational and experimental evidence remains inconclusive in this regard (Baran et al., 2016; Cherdieu et al., 2014; Eggert et al., 2013; Mazzoni et al., 1999; Paßmann et al., 2016; Scullin, 2012; Seeck-Hirschner et al., 2012). We argue that these inconsistencies may be resolved by broadening the research focus and taking the coordinated interplay of oscillatory phenomena (Helfrich et al., 2018; cf. *Paper IV*), the

role of neurochemicals (Garrido et al., 2012; Lupien et al., 1998; Schliebs & Arendt, 2006), and structural and functional properties of hippocampal–neocortical brain circuits into account (Baran et al., 2016; Helfrich et al., 2018; Mander, Rao, Lu, Saletin, Lindquist, et al., 2013; Varga et al., 2016; cf. *Papers III* and *IV*).

Based on this exhaustive review of empirical evidence, the article concludes by providing a framework that explains and illustrates the mechanisms that provoke changes in memory consolidation during aging (cf. *Paper I* Figure 2 for a schematic). Importantly, and in contrast to recent literature reviews in the field, our perspective is not limited to the mere association between sleep physiology and memory consolidation (e.g., Fogel et al., 2012; Pace-Schott & Spencer, 2011; Scullin & Bliwise, 2015). Instead, we highlight that consolidation impairments in old age are linked to changes in sleep physiology but emerge in conjunction with alterations in brain structure and neurochemistry (Buckley & Schatzberg, 2005; Mander, Rao, Lu, Saletin, Lindquist, et al., 2013; Zhong et al., 2019). Overall, this results in a situation where the generation of cardinal oscillations during NREM sleep is impaired, and their interplay becomes diffuse. As a consequence, the rendering of stable episodic memory representations may be impeded (Cordi, Schreiner, & Rasch, 2018; Gerrard, Burke, McNaughton, & Barnes, 2008; Helfrich et al., 2018; Mander, Rao, Lu, Saletin, Lindquist, et al., 2013; Ward, Oler, & Markus, 1999).

The article concludes by formulating practical advice and a research agenda, both of which are considered essential for the investigation of episodic memory consolidation in aged individuals. Among others, we stress the importance of a tight control of memory encoding and retrieval processes (see *Paper III* for an application example). Moreover, age-fair analytical approaches to study sleep physiology in aged individuals are required (see *Paper II* for more details). Furthermore, studies that simultaneously incorporate different predictors for successful memory consolidation are essential (see *Paper III* and *IV* for the contribution of age-related gray matter atrophy). Finally, as a long-term goal, longitudinal approaches are desperately needed to unravel the lead–lag relation between age-related changes in brain structure, sleep, and memory consolidation.

## 4.2 Paper II: Identification of Methodological Challenges in Research on Sleep and Aging

**Muehlroth, B. E.**, & Werkle-Bergner, M. (2019). Studying the interplay of sleep and aging: Methodological challenges. *bioRxiv,* 713552. doi: 10.1101/713552.

In this article, we build upon one of the demands postulated above, that is the need to develop age-fair analytic tools for the study of sleep physiology in older adults. Based on collected PSG and structural MRI data, we pinpoint and illustrate methodological core challenges in the study of sleep and aging, and provide advice to resolve them.

### General Study Design

In an age-comparative study, 34 healthy younger adults (19–28 years) and 41 healthy older adults (63–74 years) completed an age-adapted associative memory paradigm that has recently been developed in our group (cf. Fandakova et al., 2018). In short, during a learning session on Day 1, participants were trained on an imagery learning strategy and encoded a large number of scene–word associations. Memory for these pairs was tested immediately after learning and approximately 24 hours later (Day 2) using a cued–recall task. In addition, participants' sleep was monitored at their homes the nights before and after learning using ambulatory PSG devices. Structural brain integrity was indexed by voxel-based morphometry (VBM) of structural MRI data that were acquired on Day 2.

### Summary of Contents

In the course of the article, we elaborate on five concrete methodological challenges researchers face when studying the interplay of sleep and aging. Data examples are based on the two nights of ambulatory PSG recordings in younger and older adults and structural MRI data.

***1. Ambiguous sleep stage definitions across age groups.*** These days, the scientific definition of sleep stages is based on polysomnographic recordings and relies on rules provided by the *American Academy for Sleep Medicine* (AASM; Iber et al., 2007). Sleep stages are regarded as sensitive indicators of specific electrophysiological events that typically accompany

these stages (Hobson, 1968). For instance, sleep spindles are considered cardinal to stage 2 NREM sleep, whereas slow oscillations and delta waves mark SWS. We show that the absolute slow wave amplitude criterion of 75 μV to define SWS severely biases sleep stage estimates in older adults. Older adults typically display slow wave amplitudes below this criterion (cf. Silber et al., 2007; Webb, 1982). Despite the presence of SWA, the hallmark of SWS, older adults are hence often characterized as lacking visually scored SWS and, at the same time, as displaying an increase in lighter stage 2 NREM sleep. Thus, we advise age-comparative sleep research to transcend stage-based analyses. Instead, we recommend a focus on predefined neurophysiological processes present during *both* stage 2 sleep and SWS, such as the presence of spindles and slow oscillations.

***2. Multiple ways to describe sleep physiology.*** Multiple indicators and algorithms are available to describe the dynamics and characteristics of sleep-specific neural activity. For instance, low-frequency oscillatory activity during NREM sleep can be defined based on the proportion of SWS, SWA, or the number, density, frequency, and amplitude of slow oscillations (cf. Amzica & Steriade, 1998; Mensen, Riedner, & Tononi, 2016). Here, we demonstrate that sleep-specific oscillatory properties can be reliably measured using common analytical approaches. However, the great disparity and poor agreement of the seemingly similar available indicators calls for a thorough consideration of the way sleep physiology is described and quantified (see *Paper II* Box 2 for the interpretation of frequently reported oscillatory characteristics). We argue that the comparability and validity of (age-comparative) sleep studies is contingent on the precise definition of indicators that mirror the actual *explorandum*, i.e., the neurophysiological process of interest, as directly as possible (Amzica & Steriade, 1998; Conte & Ficca, 2013; Sun et al., 2019).

***3. Amplitude reductions.*** Based on the aforementioned issues, a direct investigation of oscillatory events during sleep is inevitable. Yet, the success of this approach is constrained by lacking consensus on the applied detection thresholds. We show that, due to great age differences in slow oscillation amplitudes, only amplitude thresholds that are adjusted within individuals allow for an age-fair assessment of true slow oscillations. Absolute inter-individual differences in slow oscillation amplitudes might not always carry functionally relevant information (Dannhauer, Lanfer, Wolters, & Knösche, 2011; Dijk, Duffy, & Czeisler, 2000;

Dubé et al., 2015; Leissner, Lindholm, & Petersen, 1970). Hence, we stress that analytic pipelines that tag slow oscillations with the largest amplitudes within each individual (e.g., Klinzing et al., 2016; Mölle, Marshall, Gais, & Born, 2002; Ngo et al., 2013) are advantageous for age-fair assessments.

***4. Differential frequency shifts in sleep oscillations.*** Besides amplitude thresholds, cut-off frequencies defining oscillatory events have to be considered carefully. Frequency bands in which slow oscillations and spindles can be observed can vary between individuals and differ by age (Carrier et al., 2011; Cox, Schapiro, Manoach, & Stickgold, 2017; Purcell et al., 2017). We demonstrate that slow oscillations and slow spindles slow down with advancing age, whereas fast spindles increase their inherent frequency. To prevent that automatized detection algorithms miss true oscillatory events and mix functionally distinct oscillatory components in some age groups, individually determined frequency ranges are required (Cox et al., 2017; Ujma et al., 2015).

***5. Topographical disparities in age-related sleep changes.*** Finally, we illustrate that age differences in sleep physiology are topographically heterogeneous (Buchmann et al., 2011; Carrier et al., 2011; Kurth et al., 2010; Landolt & Borbély, 2001; Martin et al., 2013; Sprecher et al., 2016). We relate this observation to alterations in the structural integrity of the brain. For instance, age differences in the presence of fast spindles were maximal over frontal brain regions that show the earliest and strongest decline in gray matter (Giorgio et al., 2010; Raz & Rodrigue, 2006). We argue that the observed topographical heterogeneity of measured age differences suggests that oscillatory events may not always be globally reduced in older adults. Rather, the propagation of, *per se*, normally generated sleep oscillations may be affected during aging (Dubé et al., 2015; Mander, Rao, Lu, Saletin, Lindquist, et al., 2013).

Based on the defined challenges, the article concludes that the development of age-fair and individualized analytic procedures that filter out age-independent inter-individual differences and age-related confounding factors is required (Molenaar & Campbell, 2009; Nesselroade et al., 2007). These age-adapted methodological approaches are needed to uncover true age-dependent alterations in the physiology of sleep, and to foster the development of valid and reliable biomarkers of age-associated cognitive pathologies.

### 4.3 Paper III: Identification of the Role of Memory Quality for Memory Consolidation

**Muehlroth, B. E.**, Sander, M. C., Fandakova, Y., Grandy, T. H., Rasch, B., Shing, Y. L., & Werkle-Bergner, M. (2019). Memory quality modulates the effect of aging on memory consolidation during sleep: Reduced maintenance but intact gain. *bioRxiv,* 547448. doi: 10.1101/547448.

In this paper, age differences in memory consolidation were examined conditional on each memory's encoding quality. Multivariate statistical tools (Partial Least Squares Correlation [PLSC]; Haenlein & Kaplan, 2004; Krishnan, Williams, McIntosh, & Abdi, 2011; McIntosh & Bookstein, 1996) were used to relate concomitant alterations in sleep physiology and brain structure – characteristic for increasing age – to changes in memory performance across sleep.

#### Theoretical Background

Despite the striking parallelism of age-related changes in sleep and memory, research is inconclusive as to whether and under which circumstances memory consolidation is impaired in late adulthood (Scullin & Bliwise, 2015). This might be due to unrecognized variation in memory *quality* or *strength* that can be discriminated based on the depth of encoding (Craik & Lockhart, 1972) and degree of learning (Tulving, 1967). Critically, memory consolidation during sleep is assumed to be an active and selective process (Diekelmann, Wilhelm, & Born, 2009; Stickgold & Walker, 2013). It may rely upon initial learning success (Conte & Ficca, 2013; Sonni & Spencer, 2015; Wilson et al., 2012) and have a primary role in maintaining successfully but not sufficiently encoded memories (e.g., Drosopoulos, Schulze, Fischer, & Born, 2007; Schoch, Cordi, & Rasch, 2017; Stickgold, 2010; Stickgold & Walker, 2013). We assume that concomitant age-related changes in sleep oscillations during NREM sleep (Mander et al., 2017, for a review) and structural properties of the brain (Fjell & Walhovd, 2010; Raz et al., 2005; Raz & Rodrigue, 2006; Ziegler et al., 2012) may account for potential deficits in these active consolidation processes in later life (Harand et al., 2012; Hornung et al., 2005).

**Methods**

Repeated cued-recall phases during learning on Day 1 were used to track the fate of single scene–word associations within individuals (cf. Dumay, 2016; Fenn & Hambrick, 2013; Schreiner et al., 2018). Based on recall success across the repeated learning instances, it was possible to separately investigate memory consolidation conditioned on different levels of encoding quality. Indicators of NREM sleep were extracted using power spectral analysis to estimate SWA (0.5–4.5 Hz) and applying established detection algorithms to define slow oscillations (0.5–1 Hz), slow (9–12.5 Hz), and fast spindles (12.5–16 Hz; Klinzing et al., 2018, 2016; Mölle et al., 2011, 2002; Ngo et al., 2013). PLSC (Haenlein & Kaplan, 2004; Krishnan et al., 2011; McIntosh & Bookstein, 1996; McIntosh & Lobaugh, 2004; McIntosh & Mišić, 2013) was applied to overcome the typical use of multiple bivariate correlations by integrating *patterns* of sleep physiology and brain structure typical for advancing age. Finally, we examined how the senescent sleep and brain structure profiles derived in this way relate to inter-individual differences in memory consolidation.

**Major Findings**

The extent of age-related impairments in memory consolidation was dependent on each memory's encoding quality: Whereas the overnight gain of mnemonic associations unavailable before sleep was similar in younger and older adults, the maintenance of successfully learned associations across sleep was reduced in older adults. Deficits in memory maintenance were most pronounced for mnemonic contents of intermediate encoding quality. Across age groups, both an 'aged' sleep profile, defined by decreased SWA, a reduced presence of slow oscillations, slow, and fast spindles, and an 'aged' brain structure profile, characterized by gray matter reductions in the medial prefrontal cortex (mPFC), thalamus, entorhinal cortex, and hippocampus, were associated with reduced memory maintenance. Still, within age groups, neither inter-individual differences in NREM sleep physiology nor in structural brain integrity could account for the observed inter-individual variation in memory consolidation. We suggest that a mechanistic understanding of the precursors of memory consolidation ultimately requires novel analytic tools that elucidate the fine-tuned interplay between NREM-specific oscillatory components (cf. *Paper IV*).

## 4.4 Paper IV: Identification of the Role of Slow Oscillation–Spindle Coupling for Memory Consolidation

**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,* 1940. doi: 10.1038/s41598-018-36557-z.

In this article, the temporal coordination of slow oscillations and sleep spindles was taken into account. Age differences in slow oscillation–spindle coupling were examined and related to overnight memory retention and structural brain integrity, respectively.

### Theoretical Background

According to system consolidation theory (Born & Wilhelm, 2012), the concerted interplay of brain rhythms during NREM sleep facilitates memory consolidation during sleep (Diekelmann & Born, 2010; Marshall & Born, 2007; Steriade, 2006). Neocortical slow oscillations precisely time the hippocampal reactivation of previously acquired mnemonic contents with the occurrence of fast thalamo-cortical sleep spindles (Clemens et al., 2011; Diekelmann & Born, 2010; Klinzing et al., 2016; Staresina et al., 2015; Steriade, 2003). In contrast to the strong theoretical emphasis on their interplay, most empirical evidence so far has focused on the independent contribution of slow oscillations and sleep spindles to memory consolidation. Especially in humans, the premises and consequences of this dynamic oscillatory interplay have remained largely unknown. We assume that, as a consequence of brain aging, not only slow oscillation and spindle generation and propagation (Dubé et al., 2015; Fogel et al., 2012, 2017; Mander, Rao, Lu, Saletin, Lindquist, et al., 2013), but also their coordination may be critically impaired. In turn, this may result in reduced overnight memory consolidation (Helfrich et al., 2018; Ladenbauer et al., 2017).

### Methods

To identify and compare age-typical slow oscillation–spindle coordination, PSG data were investigated in two ways: (1) We examined the temporal association of extracted slow oscillation

and spindle events, and (2) analyzed oscillatory power present during slow oscillations by means of time–frequency analyses. Associations between the hereby defined slow oscillation-specific time–frequency characteristics and memory consolidation were established using a cluster-corrected correlation approach (Maris & Oostenveld, 2007). We used the same approach to determine whether inter-individual variation in slow oscillation–spindle coupling relates to structural integrity in source regions of slow oscillation and spindle generation and key regions of memory processing.

**Major Findings**

Consistent with previous literature (e.g., Klinzing et al., 2016; Mölle et al., 2011; Staresina et al., 2015), slow oscillations and sleep spindles were precisely timed in younger adults. Fast sleep spindles were locked to the slow oscillation peak and slower spindles to the up- to down-state transition. In old age, however, fast spindles power increases during the up-state of slow oscillations were reduced and peaked before the slow oscillation peak. In contrast, slow spindle power increases at the end of the slow oscillation up-state became more pronounced. In younger adults, the increase in slow spindle power typical for older adults correlated with worse overnight memory retention. A 'youth-like' precision of fast spindles coupled to the slow oscillation peak related to better memory consolidation across both younger and older adults. Finally, in old age, gray matter volume in the mPFC, thalamus, entorhinal cortex and hippocampus was associated with a more 'youth-like' modulation of spindle activity during slow oscillations. We interpret these results within the framework of 'brain maintenance' (Cabeza et al., 2018; Nyberg et al., 2012) and speculate that the success of memory consolidation in old age is ultimately determined by maintained structural integrity and a preserved interplay of oscillatory events during NREM sleep.

# 5 Discussion

In the following, I will summarize, assess, and interpret the main findings of *Papers II*, *III*, and *IV* with respect to previous literature and the theoretical framework developed in *Paper I*. I will then discuss the potentials and limitations of the current work and provide future research perspectives.

## 5.1 Evaluation of Major Findings

### 5.1.1 Memory Maintenance Is Selectively Impaired in Older Adults

To answer the question whether memory consolidation is affected by aging, first and foremost, fair learning conditions for both younger and older adults are required (Conte & Ficca, 2013; Rugg & Morcom, 2005). In *Paper III* and *IV* we demonstrate that older adults are capable of learning a presented set of picture–word associations to a similar level as younger adults – at least if the difficulty of the memory paradigm is adjusted for each age group. Similar task demands were achieved by adapting the number of associations to be learned (i.e., the *memoranda*) and the number of cued-recall blocks with feedback during learning (cf. Daselaar, Fleck, Dobbins, Madden, & Cabeza, 2006; Duverne, Habibi, & Rugg, 2008; Morcom, Li, & Rugg, 2007). Also, prior training of an imagery learning strategy ensured similar engagement in strategic processes during encoding across age groups (Naveh-Benjamin, 2000; Naveh-Benjamin et al., 2007; Shing et al., 2008). But even when overall learning success was initially comparable between younger and older adults, older adults subsequently retrieved fewer of the successfully learned associations on the next day, indicating that their consolidation was impaired.

The finding of diminished overnight memory retention in old age is in line with several studies reporting impaired consolidation of episodic memories during sleep in old age (e.g., Cherdieu et al., 2014; Mander, Rao, Lu, Saletin, Lindquist, et al., 2013; Scullin, 2012; Scullin, Fairley, Decker, & Bliwise, 2017; Varga et al., 2016; see *Paper I* for more details). In a meta-analysis of 15 studies, Gui et al. (2017) reported reduced beneficial effects of a night's sleep in older compared to younger adults for declarative memory contents. However, as will be discussed below, some studies suggest that the consolidation of declarative memories may

be spared from aging effects – at least under certain conditions (Aly & Moscovitch, 2010; Backhaus et al., 2007; Sonni & Spencer, 2015; Wilson et al., 2012). For instance, Sonni and Spencer (2015) showed that sleep was beneficial for buffering retrieval performance in an object location task against task-related interference – in both younger and high-performing older adults. When looking at low-performing older adults, though, this sleep benefit was not observed.

*Paper III* argues that unaccounted variation in the *quality* of individual memories could offer an explanation for these inconsistencies in the literature. We demonstrate that the extent of age differences in memory consolidation is determined by a memory's initial encoding quality. More precisely, the *maintenance* of previously successfully learned picture–word associations (i.e., medium- and high-quality memories) was reduced in older compared to younger adults. In contrast, the overnight *gain* of word–scene combinations not recalled before sleep (i.e., low-quality memories) was equal across age groups. Most crucially, deficits in maintaining associations across sleep were most pronounced for memories of *intermediate* encoding quality, that is, memories that were only acquired at the end of the learning task on Day 1.

These results substantiate the notion that memory consolidation is an active and selective process that mainly supports the maintenance and stabilization of previously successfully encoded declarative memories (Fenn & Hambrick, 2013; Nettersheim, Hallschmid, Born, & Diekelmann, 2015; Schreiner et al., 2018; Stickgold & Walker, 2013). The findings are in line with the assumption that pre-sleep encoding success determines whether age-related deficits in memory consolidation become evident (Sonni & Spencer, 2015; Tucker, McKinley, & Stickgold, 2011; Wilson et al., 2012). Memories of intermediate encoding quality might have the necessary, but not yet sufficient strength to be preferentially reactivated and redistributed during ensuing sleep (Diekelmann et al., 2009; Rasch & Born, 2013; Schapiro et al., 2017; Schapiro, McDevitt, Rogers, Mednick, & Norman, 2018; Stickgold, 2010). Since these processes of memory reactivation and reorganization are particularly disrupted in old age (Cordi et al., 2018; Gerrard et al., 2008; Helfrich et al., 2018; cf. *Paper I*), pronounced age-related impairments in memory retention, as displayed here, might be the consequence.

In sum, the findings of *Paper III* highlight that variation in the quality of individual memories can account for differential effects of aging on overnight changes in memory

performance. A tight control of learning success and avoidance of average net measures of memory performance are thus needed (Tulving, 1964, 1967).

### 5.1.2 The Rate and Coordination of Slow Oscillations and Sleep Spindles Differ By Age

The neural mechanisms driving the observed deficits in memory maintenance may rely on age-related alterations in NREM sleep (Hornung et al., 2005; Mander et al., 2017). *Papers II*, *III*, and *IV* show that alterations in sleep physiology associated with aging extend beyond the overall distribution of sleep stages and the characteristic drastic reduction of visually scored SWS (Mander et al., 2017; Ohayon et al., 2004). Even when applying age-fair detection criteria (cf. *Paper II*), SWA and the rate of frontal slow oscillations, frontal slow spindles, and central fast spindles were significantly reduced in older adults (Carrier et al., 2011; Crowley et al., 2002; Dubé et al., 2015). These alterations, as highlighted in *Paper III* by the use of PLSC (Haenlein & Kaplan, 2004; Krishnan et al., 2011; McIntosh & Bookstein, 1996), are not independent but occur in parallel. As shown, advancing age is characterized by simultaneous reductions in multiple NREM-specific oscillatory components of memory consolidation. Hence, our results underscore age-related alterations in core markers of NREM sleep physiology (see Mander et al., 2017, for a recent review) even under optimal and age-fair detection and analysis procedures.

In the active system consolidation account, the dynamic nature of oscillatory components during NREM sleep is considered pivotal (Diekelmann & Born, 2010; Klinzing et al., 2019; Marshall & Born, 2007; Steriade, 2006). Based on the notion that slow oscillations and spindles concomitantly change during aging, *Paper IV* takes their temporal coordination into consideration. We show that, besides the mere occurrence of slow oscillations and spindles, their precisely timed interplay is affected as humans age. The results of *Paper IV* support evidence that in younger adults thalamo-cortical fast spindles emerge during the hypopolarized up-states of neocortical slow oscillations (Clemens et al., 2011; Crunelli et al., 2018; Klinzing et al., 2016; Mölle et al., 2011, 2002; Staresina et al., 2015; Steriade, 2003, 2006). In older adults, though, this precise coordination dispersed: Fast spindles power was globally reduced and increased most strongly *before* the slow oscillation peak. In contrast, slow spindle power increases at the end of the slow oscillation up-state became even more pronounced in older adults (cf. Helfrich et al., 2018; Ladenbauer et al., 2017). Together with Helfrich et al. (2018), we are the first to

describe these shifts in slow oscillation–spindle coupling in old age. Potential premises and consequences of this spindle misalignment, including alterations in cerebral structure (cf. Raz et al., 2005; Raz & Rodrigue, 2006) and changes in the ability to retain memories across sleep (cf. Gui et al., 2017), are discussed below.

### 5.1.3 Brain Structure and Sleep Physiology Concomitantly Change in Aging

In all four of the publications of this dissertation, a strong emphasis is placed on the fact that alterations in sleep physiology do not occur in isolation (Zhong et al., 2019). Senescent changes in sleep physiology may arise as a consequence of alterations in the structural integrity of brain areas involved in slow wave and spindle generation and propagation (Dubé et al., 2015; Fogel et al., 2017; Helfrich et al., 2018; Landolt & Borbély, 2001; Mander, Rao, Lu, Saletin, Lindquist, et al., 2013; Saletin, van der Helm, & Walker, 2013; Varga et al., 2016; Zhong et al., 2019).

*Paper II* highlights that structural changes in the aging brain (eg., Buckner, 2004; Cabeza et al., 2005; Fjell & Walhovd, 2010; Fjell et al., 2013; Raz et al., 2005; Raz & Rodrigue, 2006; Ziegler et al., 2012) may mirror alterations in both the generation and propagation of NREM-specific oscillatory components. *Paper III* shows that participants with a pattern of reduced structural brain integrity in the mPFC, thalamus, hippocampus, and entorhinal cortex also exhibited a more senescent NREM sleep profile. As demonstrated in *Paper IV*, when older adults maintained structural integrity in these source regions of slow oscillation and spindle generation (e.g., Nir et al., 2011; Steriade et al., 1993; Steriade, 2003, 2006), the temporal coupling of fast spindle activity to the slow oscillation peak was more precise. These findings are in line with Helfrich et al. (2018), who demonstrated a link between mPFC volume and an accurate phase–amplitude coupling of slow oscillations and fast spindles. Brain integrity in the mPFC, thalamus, and MTL structures may be the foundation for an effective 'youth-like' fine-tuned coordination of slow oscillations and sleep spindles. When gray matter in these regions is strongly reduced, as is the case in aging, the precisely timed coordination of slow oscillations and spindles might disperse.

### 5.1.4 Sleep Physiology Constitutes a Potential Pathway for Age-Related Impairments in Memory Consolidation

As discussed above, aging coincides with impaired maintenance of previously learned information, altered NREM sleep physiology, and widespread gray matter atrophy. Nevertheless, the most essential question remains to be answered: Can altered sleep act as an explanation for age-related episodic memory decline? And, if so, what are the neural mechanisms driving the association between sleep and episodic memory consolidation in the aging brain?

In *Paper III*, an 'aged' NREM sleep profile of reduced SWA, slow oscillations, slow, and fast spindles was accompanied by worse memory maintenance. This association, though, was only reliable when calculated across younger and older adults. *Paper IV* provides evidence that, across younger and older adults, a 'youth-like' precision of fast spindles coupled to the slow oscillation peak related to better memory consolidation. Moreover, in younger adults, a coupling pattern typical for older adults, marked by an increase in slow spindle power at the end of the slow oscillation up-state, was associated with worse memory consolidation (see *Paper IV* for a detailed discussion). Together, these results emphasize that between-person variation in the mere *occurrence* of slow oscillations and sleep spindles might be an inadequate predictor of inter-individual variability in memory consolidation. Rather, it is their fine-tuned *coordination* that facilitates successful memory consolidation (Cairney et al., 2018; Helfrich et al., 2018; Ladenbauer et al., 2017; Latchoumane et al., 2017; Maingret et al., 2016; Niknazar, Krishnan, Bazhenov, & Mednick, 2015).

To sum up, the results of *Papers III* and *IV* provide cross-sectional evidence that age differences in NREM sleep physiology and structural brain integrity relate to age differences in memory consolidation. As previously suggested, prominent age-related changes in NREM sleep physiology may constitute one potential causal pathway for consolidation deficits observed in old age (Harand et al., 2012; Mander et al., 2017; Scullin & Bliwise, 2015). Next, by integrating the findings discussed so far, this pathway will be described and examined in more detail.

## 5.2 Integration of Findings: A Mechanistic View on Sleep and Memory Consolidation in Old Age

In *Paper III* and *IV* we demonstrate that memory consolidation is selectively impaired in older adults with most pronounced losses in the maintenance of memories of intermediate encoding quality. *Paper II* and *III* show that NREM sleep physiology strongly changes with increasing age and that slow oscillations and sleep spindles occur less often, with reduced amplitude, and changed frequency and topography. *Paper IV* provides evidence that the fine-tuned coordination of slow oscillations and spindles disperses in old age. Across *Papers II*, *III*, and *IV*, we emphasize that these changes in sleep physiology are accompanied by widespread gray matter loss in sleep- and memory-relevant brain areas. Notably, *Paper IV* shows that these structural alterations are associated with the precision of slow oscillation–spindle coupling in old age. Finally, *Papers III* and *IV* demonstrate that the overall NREM sleep profile did not fully account for inter-individual differences in memory consolidation. However, the precise coordination of slow oscillations and spindles appeared to be predictive of these differences. In the following, I will integrate these results within the theoretical framework outlined in *Paper I* (see Figure 2 of *Paper I* for a schematic). With this, I indent to offer a holistic mechanistic explanation of the neural processes driving age-related alterations in memory consolidation during sleep.

Structural brain changes observed during aging may lay the ground for dysfunctional sleep-associated memory consolidation in old age. On the one hand, they may hamper the generation and coordination of NREM-specific oscillatory components (Dubé et al., 2015; Fogel et al., 2012, 2017). On the other hand, they may directly impact memory-relevant brain circuits involved in the formation, transformation, and integration of memory representations (Eichenbaum, 2017; Genzel et al., 2017; Persson et al., 2012; Preston & Eichenbaum, 2013; Shing et al., 2010; Simons & Spiers, 2003; Wang et al., 2010). Pronounced gray matter loss in frontal brain areas and memory-relevant regions in the MTL (Fjell & Walhovd, 2010; Giorgio et al., 2010; Persson et al., 2012; Raz et al., 2005; Raz & Rodrigue, 2006; Shing et al., 2011; Ziegler et al., 2012; *Papers II* and *III*) may impede the hippocampal reactivation of memories during sleep and their redistribution among brain systems (Cordi et al., 2018; Gerrard et al., 2008; Helfrich et al., 2018; Mander, Rao, Lu, Saletin, Lindquist, et al., 2013; Ward et al.,

1999; *Paper IV*). Moreover, gray matter loss in the mPFC may impair and alter the initiation of slow waves and slow oscillations (Mander, Rao, Lu, Saletin, Lindquist, et al., 2013; Mander et al., 2015, 2017; Varga et al., 2016; *Paper IV*). Due to hippocampal and thalamic atrophy, the occurrence of sharp-wave ripples and spindles also appears to change in older adults and becomes less frequent (Nicolas, Petit, Rompré, & Montplaisir, 2001; Purcell et al., 2017; Wiegand et al., 2016; *Papers II*, *III*, and *IV*). As a consequence, attenuated slow oscillations may lose their ability to orchestrate sharp-wave ripples and spindles (Helfrich et al., 2018; Kouvaros, Kotzadimitriou, & Papatheodoropoulos, 2015; *Paper IV*). Together, this may result in an off-tune hippocampal–neocortical dialogue and, thus, in an incomplete reorganization and stabilization of memory traces during NREM sleep (Cordi et al., 2018; Gerrard et al., 2008; Mander, Rao, Lu, Saletin, Lindquist, et al., 2013; Ward et al., 1999). At the same time, SWA during deep NREM sleep is typically assumed to promote homeostatic synaptic downscaling by which redundant memory traces are erased (Cirelli, 2017; De Vivo et al., 2017; Nere et al., 2013; Tononi & Cirelli, 2006, 2014, 2016). Hypothetically, together with diminished SWA in older adults, the described mechanisms may result in a situation where (redundant) prior memory traces remain primarily reliant on the hippocampus. This may increase interference during encoding and impede subsequent learning (Mander, Rao, Lu, Saletin, Ancoli-Israel, et al., 2013; van der Werf et al., 2009; Wilson, Gallagher, Eichenbaum, & Tanila, 2006).

To conclude, based on the results obtained within this dissertation, I propose that aging involves a cascade of neural alterations that *en masse* result in an insufficient transformation and stabilization of episodic memories during sleep. The mechanistic framework I have outlined above provides orientation and guidance for future studies aiming to unravel the triad of memory, sleep, and aging. However, given the currently available evidence, to some extent, the assumptions remain speculative. Below, I will address these limitations, formulate open research questions, and provide future research perspectives.

## 5.3 Limitations and Open Questions

### Challenges of Studying Sleep and Memory

This dissertation has put a strong focus on age-fair methodological approaches in research linking sleep and memory. Still, some challenges arising when studying the association between sleep and memory consolidation remain to be resolved.

Research is immensely challenged by the difficulty to directly measure memory consolidation (cf. Conte & Ficca, 2013; Shanahan et al., 2018; Wang et al., 2019). Phases of consolidation are embedded within the whole mnemonic process and are normally assessed as a function of prior encoding and later retrieval. The age-adapted associative memory paradigm used in *Paper III* and *IV* equated age groups in their relative learning performance. This ruled out age differences in overnight memory retention due to insufficient learning. However, observed impairments in delayed memory recall could also be ascribed to retrieval processes that are known to be affected during aging (e.g., Burke & Light, 1981; Cohn et al., 2008; Craik & McDowd, 1987). Despite general availability and successful consolidation of a memory trace, older adults might not be able to access a given memory – especially when retrieval demands are high and strategic control is required (Burke & Light, 1981; Craik & McDowd, 1987; Danckert & Craik, 2013; Fandakova et al., 2018; Habib & Nyberg, 2007; Raaijmakers & Shiffrin, 1981; Shing et al., 2010). By comparison of different retrieval modes (e.g., recall vs. recognition; e.g., Danckert & Craik, 2013; Habib & Nyberg, 2007; Schoch et al., 2017), future research can disentangle whether performance differences observed during delayed recall reflect impaired *consolidation* or impaired *retrieval* of successfully consolidated memories.

By repeated test-study phases, memories are strengthened and undergo rapid online consolidation processes (Antony, Ferreira, Norman, & Wimber, 2017; Brodt, Gais, Beck, Erb, & Scheffler, 2018; Himmer, Schönauer, Heib, Schabus, & Gais, 2019; Rowland, 2014; Sutterer & Awh, 2016). Hence, these memories may already largely depend on the neocortex, rendering the beneficial effect of sleep-associated system consolidation redundant or invisible (Himmer, Müller, Gais, & Schönauer, 2017; Himmer et al., 2019; Schoch et al., 2017). To define the pace of memory consolidation for single memories, methods have to be deployed that facilitate tracking of the evolution of their neural correlates, the memory traces, themselves. Methods that

hold the promise of achieving this aim include multivariate analyses of neural activity patterns evoked by a certain memory or the identification of microstructural modifications in response to an experience (Brodt et al., 2018; Josselyn et al., 2015; Kitamura et al., 2017; Kriegeskorte & Kievit, 2013; Kriegeskorte et al., 2008; Tonegawa et al., 2015). By assessing how these measures change over time, we may be able to track changes in a memory's differential reliance on hippocampal and neocortical brain systems.

Albeit the results of *Paper III* and *IV* can well be placed within the literature on sleep-associated memory consolidation in aging, memory consolidation is not restricted to sleep (Axmacher et al., 2009). Irrespective of sleep, alterations and constraints in synaptic potentiation and plasticity (Lynch et al., 2006), hippocampal dysfunction (Ward et al., 1999), and overall impaired memory replay (Gerrard et al., 2008) may affect the generation and stabilization of memory representations (e.g., Baran et al., 2016; but see Craig et al., 2016, for comparable memory consolidation during wakeful rest in younger and older adults). Proper wake comparisons and methods to manipulate NREM sleep within participants are required to disentangle and identify the neural mechanisms that drive memory consolidation during wakefulness or sleep, respectively (Bellesi et al., 2014; Marshall & Campos-Beltrán, 2017; Wilckens, Ferrarelli, et al., 2018).

Finally, the presented work is limited by its strong focus on NREM sleep. Rather than having a unique beneficial role for declarative memories, it is currently assumed that REM sleep may potentiate memories that have been reactivated during preceding NREM phases (Cordi et al., 2014; Diekelmann & Born, 2010; Navarro-Lobato & Genzel, 2018; Power, 2004; Rasch et al., 2007; Siegel, 2001; Smith, 2001; Tononi & Cirelli, 2016; Vertes & Eastman, 2000). Its memory benefit may thus only become evident when succeeding and dynamically interacting with prior phases of NREM sleep (Ackermann & Rasch, 2014; Ambrosini & Giuditta, 2001; Giuditta et al., 1995). Beyond a continued focus on NREM sleep, theories and analysis methods should take the cyclic nature of NREM and REM sleep into account and consider their dynamic contributions (Scullin & Gao, 2018; e.g., by investigating stage transition rates, probabilities, and their temporal pattern; cf. Kishi et al., 2011; Schlemmer, Parlitz, Luther, Wessel, & Penzel, 2015; Yetton, McDevitt, Cellini, Shelton, & Mednick, 2018).

**General Limitations of Cross-Sectional Study Designs in Consolidation Research**

A major limitation of this dissertation is its exclusive reliance on cross-sectional correlational evidence. Brain and cognition are highly dynamic and vary both on the short- and long-term (Lindenberger et al., 2006; Lindenberger & von Oertzen, 2006). However, the study design applied in this dissertation neither informs us about long-term changes in aging, nor does it allow for testing how short-term within-person variability in sleep relates to memory consolidation.

To date, it has frequently been proposed that intra-individual variation in sleep might be more predictive of an individual's memory consolidation than inter-individual differences in sleep physiology (Ackermann et al., 2015; Schabus et al., 2004, 2008; Schabus, 2009; Spiegel, Koberle, & Allen, 1986). Rather than being stable, memory consolidation could represent a variable process that is modulated by intra-individual fluctuations in sleep physiology. In combination with structural and functional brain prerequisites, this variation might shape the success of memory consolidation within each individual. For instance, Schabus et al. (2004) reported that increases in spindle activity across two experimental nights (i.e., between the nights before and after encoding 160 word pairs) were positively associated with overnight memory retention. Short-term variation in sleep and memory over a single night might be relatively small, though (Buckelmüller, Landolt, Stassen, & Achermann, 2006; Schabus et al., 2008; Tucker, Dinges, & Dongen, 2007). By comparing sleep and wake intervals or manipulating specific oscillatory components during sleep, intra-individual variation can be induced and, potentially, corresponding alterations in memory consolidation revealed (Barham et al., 2016; Bellesi et al., 2014; Marshall & Campos-Beltrán, 2017; Wilckens, Ferrarelli, et al., 2018; Zhang & Gruber, 2019).

Crucially, not only on a short time scale, but in particular on the long-term – that is, across the lifespan – sleep and memory change considerably (Craik & Bialystok, 2006; Ohayon et al., 2004; Purcell et al., 2017; Shing et al., 2010). However, research has to acknowledge that, theoretically and methodologically speaking, cross-sectional age comparisons cannot inform about age-related *changes* (Hertzog & Nesselroade, 2003; Hofer & Sliwinski, 2001; Li & Schmiedek, 2002; Lindenberger & Pötter, 1998; Lindenberger et al., 2011; Overton, 2010; Raz & Lindenberger, 2011; Rönnlund et al., 2005; Wohlwill, 1970; see *Paper II* for more details).

Approximation of longitudinal change by means of cross-sectional age comparisons may be impeded by cohort effects or sampling bias (Hertzog & Nesselroade, 2003; Lindenberger et al., 2011; Wohlwill, 1970). Accordingly, reported age differences in sleep and memory should not be equated with 'real' aging in terms of longitudinal change (e.g., Rönnlund et al., 2005; Scullin & Gao, 2018). In order to study both short- and long-term dynamics of sleep and memory, research has to shift its focus on the individual and deploy longitudinal study designs (Molenaar & Campbell, 2009; Nesselroade et al., 2007; Nesselroade & Molenaar, 2016; Rose, Rouhani, & Fischer, 2013; see *Paper II* for more details). A framework that includes reciprocal and concomitant alterations in brain structure and function, sleep physiology, and memory consolidation, requires longitudinal study designs that have the potential to unravel lead–lag relationships. Until then,*"[t]he unresolved, "million dollar question," is whether sleep micro- and macro-architecture determine how well the brain/cognition are preserved in older age, or instead, whether brain/cognition preservation determines how well sleep micro- and macro-architecture are preserved."* (Scullin & Gao, 2018, p. 289).

**Future Research Perspectives**

This dissertation has established a mechanistic view on the association between sleep and episodic memory consolidation in the aging brain. The outlined framework is compatible with a long line of evidence linking sleep, episodic memory, and aging (see *Paper I* for a review on this literature). Nevertheless, some pieces of this puzzle remain missing.

As demonstrated in *Paper III*, memory consolidation is a selective process that does not support all episodic memories equally (Diekelmann et al., 2009; Saletin & Walker, 2012; Stickgold, 2010; Stickgold & Walker, 2013). However, the neural mechanisms determining this prioritization remain largely unknown and speculative (cf. Albouy et al., 2008; Benchenane et al., 2010; Bennion, Payne, & Kensinger, 2015; Heib et al., 2015; Klinzing et al., 2019; Rauchs et al., 2011). Following up on the learning trajectory of individual memories and searching for predictors of their successful retention (cf. the concept of subsequent memory effects; e.g., Werkle-Bergner et al., 2006), future research can address how memories are selected during encoding (i.e., tagged; cf. Frey & Morris, 1997; Redondo & Morris, 2011) to be preferentially consolidated.

As stressed throughout this dissertation, research on episodic memory consolidation in aging needs to acknowledge the complexity of the aging brain and the multifactorial contingency of active system consolidation processes (Diekelmann & Born, 2010; Klinzing et al., 2019; Marshall & Born, 2007). In addition to NREM sleep physiology, the crucial role of structural brain integrity has been addressed within this work. However, *Paper I* highlights that studies characterizing the contribution of age-related changes in neurochemistry and their link to memory consolidation are required (cf. Buckley & Schatzberg, 2005; Garrido et al., 2012; Lupien et al., 1998; Schliebs & Arendt, 2006; Terry & Buccafusco, 2003). The role of the brain's neurochemistry, like levels of ACh and cortisol during sleep, is a piece needed to complete the puzzle of how memory consolidation during sleep changes with increasing age.

As hippocampus-dependent memories appear to be most sensitive for the beneficial effects of sleep (Albouy et al., 2008; Diekelmann et al., 2009; Marshall & Born, 2007; Rauchs et al., 2011), research on sleep-associated consolidation preferentially focuses on associative memory tasks with an explicit learning mode, involving word lists almost exclusively (Greene, 2007; Holdstock, Mayes, Gong, Roberts, & Kapur, 2005; Spencer, Sunm, & Ivry, 2006; Studte, Bridger, & Mecklinger, 2015; van der Helm, Gujar, Nishida, & Walker, 2011). Whether results can be generalized to other declarative hippocampus-dependent memory tasks (e.g., spatial memory tasks), is yet to be proven. Also, it remains to be elucidated how different declarative memory domains, that is the episodic and semantic memory system, interact during memory consolidation – and how this interplay is affected during aging (Kurdziel, Mantua, & Spencer, 2017; Lewis & Durrant, 2011; Umanath & Marsh, 2014). Moreover, how findings relate to other memory domains, like procedural memory, remains to be clarified (e.g., Fogel et al., 2014; Gudberg, Wulff, & Johansen-Berg, 2014; Mander et al., 2017). To prove the general validity of the proposed mechanistic pathways that define whether sleeping benefits memory functions, future research needs to evaluate differences between diverse memory systems and subsystems (e.g., declarative vs. non-declarative memory; associative vs. item memory; motor learning vs. motor adaptation).

# 6 Synthesis: A Lifespan Perspective on Sleep-Associated Memory Consolidation

Altogether, this dissertation accomplishes two main objectives: (1) It presents new methodological approaches to derive age-fair and sensitive sleep and memory measures and implements novel techniques to link them. (2) On this basis, this work advances our theoretical understanding of the neural processes that account for impaired memory consolidation in older adults. It uses multivariate tools to study interdependent alterations in sleep physiology during aging, focuses on the precise coordination of these processes, and takes the role of structural brain integrity into account. Thereby, potential candidate processes are revealed that determine how youth-like memory consolidation is maintained in senescence. Together, this dissertation enriches and advances the active system consolidation account and complements and refines previous theories on memory aging.

As the theoretical basis for this dissertation, I took a lifespan perspective on brain and cognition (Baltes et al., 1980, Baltes, 1987; Baltes et al., 1998, 1999; Craik, 2006; Lindenberger et al., 2006). Aging was viewed as the result of infant development, lifelong dynamic brain–behavior–environment interactions, and the onset and progression of (non-)pathological aging processes (Buckner, Head, & Lustig, 2006; Li, 2003; Lindenberger et al., 2006; Troen, 2003). Sleep-associated episodic memory consolidation was chosen as a model to illustrate the methodological intricacies and emphasize the scientific gains that emerge when applying an aging perspective to cognitive neuroscience (Lindenberger et al., 2006, 2011). Aging, as studied within this dissertation, was chosen as an illustrative period of cognitive and neural reorganization and transformation. Childhood ontogenetic development was not addressed in this work, although it represents a pivotal period during which the brain and cognition are decisively formed (Karmiloff-Smith, 1997, 1998; Munakata, Casey, & Diamond, 2004; Schwabe, Joëls, Roozendaal, Wolf, & Oitzl, 2012; Temple, 1997; Wilhelm, Prehn-Kristensen, & Born, 2012). To complement the lifespan perspective on cognitive neuroscience, infant development needs to be included as the starting point and basis of lifelong dynamic brain–behavior–environment interactions (Baltes et al., 1998; Li, 2003; Lindenberger et al., 2006). This opens avenues that can give rise to more universal and integrative frameworks to

explain and comprehend cognition (e.g., Sander, Lindenberger, & Werkle-Bergner, 2012; Shing et al., 2010).

The result obtained in this work hold the potential to refine our general perspective on age differences in episodic memory function. In their traditional views, theories on memory-relevant PFC–MTL interactions (e.g., Eichenbaum, 2000, 2017; Moscovitch et al., 2016; O'Reilly & Norman, 2002; Preston & Eichenbaum, 2013; Simons & Spiers, 2003) and on memory and aging (e.g., Anderson et al., 2000; Craik & Rose, 2012; Habib et al., 2003; Naveh-Benjamin et al., 2007; Shing et al., 2008, 2010), have put a strong focus on memory encoding and retrieval. Within this dissertation I demonstrate that, even when hippocampal–prefrontal memory circuits successfully guide the encoding and retrieval of mnemonic contents (Shing et al., 2010; Simons & Spiers, 2003), active consolidation processes that rely on the same brain networks can be impaired (e.g., Baran et al., 2016; Mander, Rao, Lu, Saletin, Lindquist, et al., 2013; *Papers III* and *IV*). As previously highlighted, *"it therefore seems necessary to acknowledge some form of post-cognitive 'consolidation' process, whose mechanism is still obscure at the human level at least."* (Craik & Bialystok, 2006, p. 890). With its focus on sleep-associated consolidation of episodic memories in late adulthood, this dissertation constitutes a first step in this direction.

Studying cognitive and neural aging has provided us with a unique chance to prove, question, and refine theoretical and methodological conventions. We are thus able to better investigate whether and how sleep physiology contributes to the stabilization and integration of memories. As already concluded by Gais and Born in their first description of the active system consolidation account in 2004, *"Regarding the ever more complex data on the association between sleep and memory, all monocausal models attributing effects to one mechanism are likely to fail, especially if they use descriptive concepts such as 'REM sleep' that represent an accumulation of many different physiological processes occurring simultaneously"* (Gais & Born, 2004, p. 684). Within this dissertation I have repeatedly emphasized the necessity to go beyond analytical and theoretical conventions in the field that merely focus on the overall structure of sleep states (Conte & Ficca, 2013; *Papers II* and *IV*). In addition, my work stresses that research methods and theories have to be evaluated thoroughly when going beyond the 'optimal' brain of a healthy younger adult. If this need is acknowledged, the application of a lifespan perspective can unfold its potential to advance our knowledge on the mechanisms

guiding active system consolidation. In turn, this will help to elucidate the neural machinery causing impaired episodic memory functioning in old age (e.g., Craik & Bialystok, 2006; Shing et al., 2010).

Certainly, applying an aging perspective to cognitive neuroscience is worth the effort, as its scientific promise is truly remarkable. If we maneuver the challenging tightrope walk between methodological intricacies and scientific potentials posed by the cognitive neuroscience of aging, we will gain a new perspective on old problems.

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# Paper I

**Muehlroth, B. E.**, Rasch, B., & Werkle-Bergner, M. (under review).
*Episodic memory consolidation during sleep in healthy aging*.

For the most recently published version [March, 2020], please see:
**Muehlroth, B. E.**, Rasch, B., & Werkle-Bergner, M. (2020).
Episodic memory consolidation during sleep in healthy aging.
*Sleep Medicine Reviews, 52*, 101304. doi: 10.1016/j.smrv.2020.101304.

# Paper II

**Muehlroth, B. E.**, & Werkle-Bergner, M. (2019).
Studying the interplay of sleep and aging: Methodological challenges.
*bioRxiv*, 713552. doi: 10.1101/713552.

For the most recently published version [January, 2020], please see:
**Muehlroth, B. E.**, & Werkle-Bergner, M. (2020).
Understanding the interplay of sleep and aging: Methodological challenges.
*Psychophysiology, 57*(3), e13523. doi: 10.1111/psyp.13523.

# Paper III

**Muehlroth, B. E.**, Sander, M. C., Fandakova, Y., Grandy, T. H.,
Rasch, B., Shing, Y. L., & Werkle-Bergner, M. (2019).
Memory quality modulates the effect of aging on memory consolidation during sleep:
Reduced maintenance but intact gain. *bioRxiv*, 547448.
doi: 10.1101/547448.

For the most recently published version [January, 2020], please see:
**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.
doi: 10.1016/j.neuroimage.2019.116490.

# Paper IV

**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*, 1940.
doi: 10.1038/s41598-018-36557-z.

# Anlage

Erklärung gemäß § 7 Abs. 3 Satz 4 der Promotionsordnung über den Eigenanteil an den veröffentlichten oder zur Veröffentlichung vorgesehenen eingereichten wissenschaftlichen Schriften im Rahmen meiner publikationsbasierten Arbeit

**I.** Name, Vorname: Mühlroth, Beate E.

Institut: Max-Planck-Institut für Bildungsforschung

Promotionsfach: Psychologie

Titel: Sleep-Associated Consolidation of Episodic Memories in Old Age – The Challenge of Studying Cognitive and Cerebral Aging

**II. Nummerierte Aufstellung der eingereichten Schriften (Titel, Autoren, wo und wann veröffentlicht bzw. eingereicht):**

1. **Muehlroth, B. E.,** Rasch, B., & Werkle-Bergner, M. (under review). Episodic memory consolidation during sleep in healthy aging.

Eingereicht am 19.10.2018 bei *Sleep Medicine Reviews*, 1. Revision eingereicht am 24.08.2019

2. **Muehlroth, B. E.**, & Werkle-Bergner, M. (2019). Studying the interplay of sleep and aging: Methodological challenges. *bioRxiv, 713552*.doi: 10.1101/713552.

Eingereicht am 28.08.2019 bei *eLife*

3. **Muehlroth, B. E.,** Sander, M. C., Fandakova, Y., Grandy, T. H., Rasch, B., Shing, Y. L., Werkle-Bergner, M. (2019). Memory quality modulates the effect of aging on memory consolidation during sleep: Reduced maintenance but intact gain. *bioRxiv, 547448*. doi: 10.1101/547448.

Eingereicht am 19.02.2019 bei *NeuroImage*, 1. Revision eingereicht am 24.08.2019

4. **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*, *9:1940.* doi:10.1038/s41598-018-36557-z

**III. Darlegung des eigenen Anteils an diesen Schriften:**

zu II. 1.:
Entwicklung der Konzeption (überwiegend), Literaturrecherche (vollständig), Erstellen des Manuskriptes (überwiegend)

zu II. 2.:
Entwicklung der Konzeption (überwiegend), Literaturrecherche (vollständig), Methodenentwicklung (überwiegend), Erstellen des Manuskriptes (überwiegend), Datenerhebung (mehrheitlich), Datenauswertung (vollständig), Ergebnisdiskussion (überwiegend), Programmierung der Analyseskripte (vollständig)

zu II. 3.:
Literaturrecherche (vollständig), Methodenentwicklung (mehrheitlich), Datenerhebung (mehrheitlich), Datenauswertung (vollständig), Ergebnisdiskussion (mehrheitlich), Erstellen des Manuskriptes (überwiegend), Programmierung der Analyseskripte (vollständig), Veröffentlichung der Daten und Skripte auf dem Open Science Framework (vollständig)

zu II. 4.:
Literaturrecherche (vollständig), Methodenentwicklung (überwiegend), Datenerhebung (mehrheitlich), Datenauswertung (vollständig), Ergebnisdiskussion (überwiegend), Erstellen des Manuskriptes (überwiegend), Revision des Manuskriptes (überwiegend), Programmierung der Analyseskripte (vollständig), Veröffentlichung der Daten und Skripte auf dem Open Science Framework (vollständig)