# SLEEP AND ITS OSCILLATORY CHARACTERISTICS IN OVERNIGHT LEARNING - WHAT IS THE ROLE OF PLASTICITY GENES *BDNF* AND *COMT*?

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# ABSTRACT

Sleep is crucial for human health and function. Decades of research have accumulated our understanding on the influence of sleep – or the lack of it – on different domains such as metabolic and brain health, immune function and cognitive performance. One of the most extensively studied topics in regards to sleep is learning and memory. Sleep not only protects memories from wake-time interference, but it also actively transfers them from temporal storage to more permanent representations in the neocortex. This consolidation process of declarative memories is believed to be facilitated by certain oscillations during non-rapid eye movement (NREM) sleep, that is, sleep spindles, slow oscillations (SO) and sharp-wave ripples. Recent experiments in humans have demonstrated the importance of inter-oscillation synchrony on memory retention.

Do all individuals equally share the memory benefits of sleep? Certain gene polymorphisms, such as *BDNF* Val66Met and *COMT* Val158Met, have been attributed with implications on synaptic plasticity, neuroanatomy and functional brain activation within memory-related brain networks. Behavioral studies have found relative mnemonic advantages to associate with the alleles that reportedly promote brain plasticity, i.e. $Val_{BDNF}$ and $Met_{COMT}$. Moreover, homeostatic sleep drive is moderated by *BDNF* Val66Met and *COMT* Val158Met. However, the role of these polymorphisms in memory retention over sleep has been scarcely studied.

In this thesis, overnight memory for verbal and visual material was studied. Specific focus was put on how sleep spindles and their phasic synchrony with slow oscillations associate with memory performance. Importantly, it was questioned whether genetic predisposition for neural plasticity (*BDNF* Val66Met and *COMT* Val158Met) interacts with overnight memory and the related consolidation mechanisms. The studies in this thesis were conducted either on an adolescent (~17 y) cohort (Glaku) or on a sample consisting of young adults. Genotypic investigations concerned the Glaku sample. Sleep was recorded with an ambulatory polysomnography in all studies.

It was found that memory outcome – both verbal cued recall and picture recognition – was strongly associated with fast sleep spindles and their accurate coupling with the depolarized 'upstate' of SOs. *BDNF* Val66Met moderated the associations between sleep oscillations and visual recognition memory. Further investigation showed that memory outcome was robustly predicted by fast sleep spindles and their SO-coupling only in $Val_{BDNF}$ homozygotes but not $Met_{BDNF}$ carriers. In addition, memory performance in

the Val$_{BDNF}$ homozygote group was seen more vulnerable to extended wake during the retention period. *COMT* Val158Met did not moderate the associations between sleep variables and recognition accuracy.

In conclusion, the thesis augments the understanding of the interplay between sleep, NREM oscillations and overnight memory. To an extent, the relation between sleep and memory may depend on inheritance. Genetic propensity for synaptic plasticity possibly enhances the effect of events that promote sleep-dependent consolidation. The findings question whether the benefits of sleep on memory are constant and equal across individuals.

# TIIVISTELMÄ

Uni on terveydelle ja toimintakyvylle välttämätöntä. Vuosikymmenten tutkimus on lisännyt tietoa unen – ja sen puutteen – vaikutuksesta lukuisiin hyvinvoinnin osa-alueisiin. Näitä ovat esimerkiksi metabolinen terveys, aivojen terveys, immuunipuolustus sekä kognitiiviset toiminnot. Eräs tutkituimmista alueista unitutkimuksessa on muisti ja oppiminen. Uni ei ainoastaan suojaa muistoja valveen aikaiselta sekoittumiselta, vaan se myös aktiivisesti siirtää niitä väliaikaisesta muistivarastosta pysyviksi edustuksiksi aivokuorelle. Tiettyjen NREM-unen (non-rapid eye movement) aikaisten oskillaatioiden, eli unisukkuloiden, hitaiden aaltojen sekä hippokampusväreiden, uskotaan aktiivisesti edistävän tätä muistojen konsolidaatioprosessia. Viimeaikaiset tutkimukset ihmisillä ovat osoittaneet, että oskillaatioiden välinen synkronia on oleellista muistojen säilymiselle.

Ovatko unen hyödyt muistitoiminnoille samat yksilöiden välillä? Tietyt geenipolymorfismit, kuten *BDNF* Val66Met ja *COMT* Val158Met, on aiemmassa tutkimuksessa yhdistetty synaptiseen plastisuuteen, aivoanatomiaan sekä -toimintaan niissä aivorakenteissa, jotka tukevat muistitoimintoja. Alleelien, joiden oletetaan edistävän aivojen plastisuutta ($Val_{BDNF}$ ja $Met_{COMT}$), on käyttäytymisen tasolla havaittu assosioituvan suhteelliseen etuun muistisuoriutumisessa. Tämän lisäksi on raportoitu, että *BDNF* Val66Met sekä *COMT* Val158Met vaikuttavat unipaineen homeostaasiin. Tästä huolimatta näiden polymorfismien roolia unen ja muistamisen yhteydessä on tutkittu vain vähän.

Tämä väitöskirja tutki kielellistä ja näönvaraista muistamista yön yli. Erityisesti keskityttiin siihen, kuinka unisukkulat sekä niiden vaihesynkronia hitaiden aaltojen kanssa assosioituvat muistisuoriutumiseen. Lisäksi tarkasteltiin, onko perinnöllinen taipumus aivojen plastisuuteen (*BDNF* Val66Met ja *COMT* Val158Met) yhteydessä yön yli muistamiseen (näönvarainen tunnistus) ja unen aikaisiin konsolidaatiomekanismeihin. Väitöskirjan tutkimukset toteutettiin joko nuorista (~17 v) koostuvassa Glaku-kohortissa tai nuorten aikuisten otoksessa. Genotyyppiin liittyvät tutkimukset koskivat Glaku-otosta. Kaikissa tutkimuksissa unta mitattiin polysomnografialla.

Väitöskirjan tutkimuksissa havaittiin, että muistitulos – sekä kielellinen, vihjeenvarainen muistaminen että kuvien tunnistus – oli selvästi yhteydessä unisukkuloihin sekä siihen, kuinka tarkasti unisukkulat ajoittuivat hitaan aallon depolarisaatiovaiheeseen. *BDNF* Val66Met moderoi unioskillaatioiden ja näönvaraisen tunnistusmuistin yhteyttä siten, että yhteys ilmeni ainoastaan $Val_{BDNF}$-homotsygooteilla, mutta ei $Met_{BDNF}$-alleelin kantajilla. Lisäksi

Val*BDNF*-homotsygooteilla runsas valve vaikutti haittaavan muistisuoriutumista. *COMT* Val158Met ei moderoinut unimuuttujien ja tunnistustarkkuuden yhteyksiä.

Tämä väitöskirja kartuttaa tietoa unesta, aivo-oskillaatioista sekä yön yli oppimisesta. Unen ja muistin yhteys saattaa jossain määrin riippua perimästä. Geneettinen taipumus synaptiseen plastisuuteen saattaa voimistaa unen aikaisten konsolidaatiomekanismien vaikutusta. Tämä kyseenalaistaa ajatuksen siitä, että unen hyödyt olisivat muuttumattomat sekä jokaiselle yhtäläiset.

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To ‘know your enemy’ perhaps best describes my path into sleep research. For me, sleep has rarely been a soft shutdown that would engulf me after a day, but a skittish bird that would take flight the instant I tried to approach it. Numerous periods of elusive sleep throughout my life have taught me to value the mysterious state and to emphatically dislike its shortage. Likely due to this personal love-hate relationship with sleep, it has always shown up as an intriguing domain of research. For the recent few years, I have had an exceptional opportunity to dig into its rich properties and unquestioned significance on human function. Here I want to express my gratitude to those who made this journey possible and enjoyable.

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Studying psychology, doing research. In my reckoning of personal history, the very beginning of those things trace back some eleven years ago to a particular turning point that would never have occurred were it not for one person. My beloved wife Susanna, you gave me the wits to see my academic aspiration and cast the confidence to pursue it. During the recent years of PhD work, you made achievements more special and some tight deadlines reachable. Thank you! Was it a coincidence that I got tempted by the puzzle called human mind? Likely not, you being a psychologist, after all, *the* clinician of this family. I have found my ambition in research, studying sleep, the mystery. Not enemy.

# CONTENTS

# LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following publications:

I Halonen, R., Kuula, L., Lahti, J., Makkonen, T., Räikkönen, K. & Pesonen, A-K. (2019). *BDNF* Val66Met polymorphism moderates the association between sleep spindles and overnight visual recognition. *Behavioural Brain Research*, 375, 112157.

II Halonen, R., Kuula, L., Lahti, J., Räikkönen, K., & Pesonen, A-K. (2021). The association between sleep-wake ratio and overnight picture recognition is moderated by *BDNF* genotype. *Neurobiology of Learning and Memory*, 177, 107353.

III Halonen, R., Kuula, L., Antila, M., & Pesonen, A-K. (2021). The Overnight Retention of Novel Metaphors Associates With Slow Oscillation–Spindle Coupling but Not With Respiratory Phase at Encoding. *Frontiers in Behavioral Neuroscience*, 15, 712774.

IV Halonen, R., Kuula, L., Lahti, J., Räikkönen, K. & Pesonen, A-K. (2022). The association between overnight recognition accuracy and slow oscillation-spindle coupling is moderated by *BDNF* Val66Met. *Behavioral Brain Research*, 428, 113889.

The publications are referred to in the text by their roman numerals.

# ABBREVIATIONS

AASM American Academy of Sleep Medicine
AMPA α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
ANOVA Analysis of variance
BDI Beck Depression Inventory
BDNF Brain-derived neurotrophic factor
COMT Catechol-O-methyltransferase
EEG Electroencephalography
EMG Electromyography
EOG Electro-oculography
FSIQ Full-scale intelligence quotient
GAD-7 General Anxiety Disorder-7
LTD Long-term depression
LTM Long-term memory
LTP Long-term potentiation
MI Modulation index
MTL Medial temporal lobe
N1–3 Stage 1–3 sleep
NMDAR N-methyl-D-aspartate receptor
NREM Non-rapid eye movement
PAC Phase-amplitude coupling
PD Propagation density
PDS Pubertal development scale
PFC Prefrontal cortex
PLI Phase lag index
PP Preferred phase
PSG Polysomnography
REM Rapid eye movement
RVL Resultant vector length
SCN Suprachiasmatic nucleus
SD Standard deviation
SHY Synaptic homeostasis hypothesis
SO Slow oscillation
STM Short-term memory
SWA Slow wave activity
SWR Sharp-wave ripple
SWS Slow-wave sleep
TIB Time in bed
TRN Thalamic reticular nucleus
TST Total sleep time
TWT Total wake time
WASO Wake after sleep onset

# 1 INTRODUCTION

Modern sleep research has distinctly demonstrated that investing time in the state of apparent shutdown leads to numerous mental and bodily benefits. One domain where sleep's significance is extensively studied is learning and memory. Being able to accumulate skills and information in a regulated fashion contributes directly to our daily function, academic success and, in the end, defines who we are. The ability of brain to preserve recently encoded memories is markedly higher over a period containing sleep, relative to staying awake. Sleeping also restores the readiness to encode new information. The understanding regarding the underlying processes and mechanisms is rapidly accumulating and gaining in accuracy, yet much remains insufficiently defined.

One sparsely studied topic is the inter-individual variability in the mechanisms of sleep-dependent memory consolidation. While the advancements in neurogenetics have elucidated how hereditary factors influence neural structure and function, the interplay between genetics, sleep and memory is relatively uncharted. Of specific interest are certain gene polymorphisms that reportedly implicate brain anatomy and synaptic plasticity, namely *BDNF* Val66Met and *COMT* Val158Met. While these polymorphisms have been associated with mnemonic functions and sleep homeostasis, research on their consequences on memory consolidation (mechanisms) during sleep has been largely nonexistent.

This thesis examines how overnight learning associates with sleep and certain oscillatory events that are considered to facilitate off-line memory consolidation, i.e. sleep spindles and their coupling with neocortical slow oscillations. It is also questioned how the gene polymorphisms *BDNF* Val66Met and *COMT* Val158Met relate with sleep oscillation characteristics and their presumed implications on overnight memory performance.

# 2 REVIEW OF THE LITERATURE

## 2.1 SLEEP

We all have extensive experience on sleep and readily recognize it as a state of immobility and reduced sensory responsiveness. We may also consent that such disconnection from environment lays a remarkable cost on productive behaviors – roughly one third of our lives are spent asleep. This cost, culminating to threats of predation and starvation, has been paid by countless lifeforms over the course of evolution. Late Dr. Allan Rechtschaffen famously speculated (Walker, 2009) whether sleep might be the biggest mistake evolution has ever made. The alternative goes that sleep must serve some vital function. Indeed, the vital function has fascinated researchers since the beginning of recorded history (Barbera, 2008). Methodological advancements during recent decades have enabled the investigation of sleep on divergent domains, such as cognition, somatic and mental health, aging, athletics and several fields of omics. It is becoming increasingly clear that sleep is quite far from being an evolutionary mistake. The following chapters describe the prevalent conceptualization of sleep, its regulation and implications on health and function.

### 2.1.1 THE REGULATION OF SLEEP

Cyclic fluctuation between active periods and rest are observable in a wide spectrum of organisms, ranging from bacteria to humans (Bhadra, Thakkar, Das, & Pal Bhadra, 2017). This suggests that powerful biological agents promote the regulation that, in turn, is timed to maximize an organism's survival and fitness in its environment (Bhadra et al., 2017). On our planet, the alternation of light and dark periods signify variation in vital factors such as foraging success, heat regulation and predatory risk. Accordingly, the most influential of environmental cues that pace the mammalian activity-rest-rhythm is light (Bhadra et al., 2017). In mammals, light stimulates retinal photoreceptor cells whose firing subsequently reaches cells in a hypothalamic structure called suprachiasmatic nucleus (SCN) (Gachon, Nagoshi, Brown, Ripperger, & Schibler, 2004). SCN is considered the primary endogenous mammalian pacemaker, a master clock that paces subsidiary oscillators in other tissues (Welsh, Takahashi, & Kay, 2010). The molecular mechanism involves an autoregulated feedback loop of gene transcription/translation where positive elements (CLOCK and BMAL1) activate negative elements (period, PER; and cryptochrome, CRY), inhibiting their own transcription (Takahashi, Hong, Ko, & McDearmon, 2008). While the feedback loop may function autonomously, light input synchronizes it with

the external world (Welsh et al., 2010). SCN input modulates melatonin production in the pineal gland, resulting in the promotion of sleep during darkness (Claustrat, Brun, & Chazot, 2005). This circadian regulation of cyclicity of sleep/wake fluctuation is known as the *Process C*, being one part of the two-process model of sleep (Borbély, 1982).

*Process S*, the counterpart in the two-process model, refers to the dynamics of homeostatic sleep pressure (Borbély, 1982). That is, sleep debt keeps accumulating when staying awake and is reduced during sleep. The neuromodulator presumed to mediate sleep need is adenosine (Porkka-Heiskanen et al., 1997). Waking activity increases the levels of cellular metabolism, which results in accumulated adenosine (Latini & Pedata, 2001) and then inhibits wake-promoting neural activity (Porkka-Heiskanen et al., 1997). A reliable indicator of the build-up of adenosine is slow-wave activity (SWA) during the subsequent sleep (Greene, Bjorness, & Suzuki, 2017). In a typical pattern of human sleep-wake behavior, the high adenosine tone in the evening interacts with the circadian regulation of melatonin secretion, thus promoting sleep (Borbély, Daan, Wirz-Justice, & Deboer, 2016).

### 2.1.2 THE ORGANIZATION OF SLEEP

Nightly sleep typically consists of different sleep stages, characterizable by specific neural activation patterns (Dang-Vu et al., 2010), electroencephalographic properties (Iber, Ancoli-Israel, Chesson, & Quan, 2007), neurotransmitter levels (B. E. Jones, 2011), changes in muscle tone (Iber et al., 2007) and hormonal activity (Morris, Aeschbach, & Scheer, 2012). The gold standard method for identifying these stages is polysomnography (PSG) that consists of electroencephalography (EEG), eye movements (electro-oculography, EOG), muscle tone (electromyography, EMG) and, depending on the objective, possibly heart activity and respiration (Marino et al., 2013). According to the American Academy of Sleep Medicine (AASM) (Iber et al., 2007), polysomnographic identifiers for non-rapid eye movement (NREM) stage 1 (N1) are slow, round eye movements, low-amplitude EEG at mixed frequencies, mainly 4–7 Hz and sharp (< 0.5 s) vertex waves. N2 sleep is recognizable by the emergence of sleep spindles and K-complexes. Sleep spindles are > 0.5 second bursts of elevated sigma (~11–16 Hz) activity. K-complexes, prominent waveforms longer than 0.5 seconds, induce a deep negative peak that is immediately followed by a positive component. The stage regarded as the state of deepest sleep is N3, i.e. slow-wave sleep (SWS). Slow oscillations (< 1.2 Hz) and delta waves (0.5–4Hz) dominate N3, but also sleep spindles keep occurring. Additionally, muscle tone is low. Finally, during rapid eye movement (REM) sleep, EOG shows symmetrical, rapid eye movements whereas muscle tone is at its lowest with occasional transient EMG bursts. EEG shows low amplitude, mixed frequencies while no sleep spindles and K-

complexes occur. The approximate proportions ford N1-3 and REM sleep are 5 %, 50 %, 20 % and 25 %, respectively (Iber et al., 2007).

During a night of sleep, the stages alternate in a cyclic fashion (Carskadon & Dement, 2011). A typical sleep cycle starts with light sleep (N1 or N2) which then deepens to SWS. After a period of SWS, NREM sleep often lightens before entering to REM sleep that concludes the cycle. The duration of one cycle is about 90 minutes and a full night of sleep contains 4–6 sleep cycles.

The relative amounts of different sleep stages per cycle do not remain stable across the night. Instead, SWS is abundant during the early part of nocturnal sleep, whereas REM sleep increases towards the morning hours (Carskadon & Dement, 2011). The reduction of SWS largely relates to the homeostatic dissipation of sleep pressure. Accordingly, the EEG power in slow-wave range, an indicator of sleep debt, is highest during the first sleep cycle and progressively decreases along the subsequent cycles (Dijk, 2009). Also REM sleep is considered homeostatically regulated (Park & Weber, 2020; Shea et al., 2008). While the molecular basis is not well-known, some evidence points at a possible role of brain-derived neurotrophic factor (BDNF) (Datta, Knapp, Koul-Tiwari, & Barnes, 2015). Finally, sleep architecture is also influenced by the circadian sleep regulation. Studies have shown that slow-wave activity (SWA) and sleep spindle activity largely coincide with the melatonin rhythm (Dijk, 2009). Additionally, the acrophase of REM sleep is timed at the early morning (Endo et al., 1981).

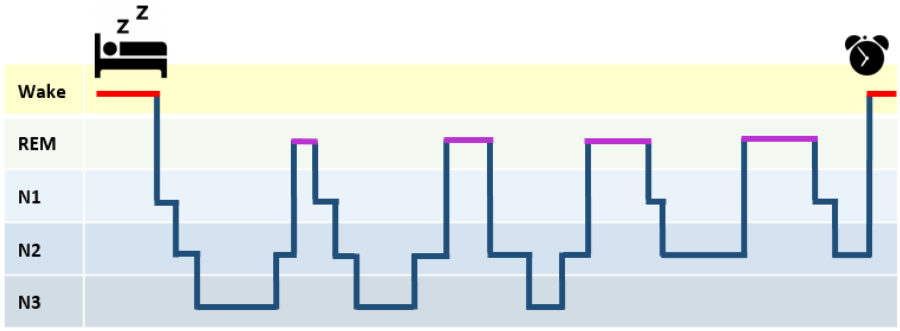


**Figure 1.** A schematic night of sleep.

### 2.1.3 WHAT IS SLEEP FOR?

The extent of sleep-dependent processes that promote success and survival is far more voluminous than is possible to unfold briefly. However, a concise overview is in order, as it helps to understand how sleep intertwines with different aspects of restoration, health and cognition.

Arguably, the most obvious consequences of sleep concern energy consumption and restoration. Evidence across different species indicate that sleep conserves energy by downregulating body temperature and metabolic rate (Berger & Phillips, 1995). Accordingly, sleep deprivation in humans has been shown to lead to increased energy consumption (Jung et al., 2011). Moreover, slow-wave activity during the initial hours of sleep is observed to recharge neuronal energy levels, thus allowing restorative biosynthetic events (Dworak, McCarley, Kim, Kalinchuk, & Basheer, 2010).

Sleep is implicated with health consequences. Studies on metabolic health have linked poor sleep with obesity (Cappuccio et al., 2008; Fatima, Doi, & Mamun, 2015), impaired appetitive evaluation (Greer, Goldstein, & Walker, 2013), inflammation (Irwin, Olmstead, & Carroll, 2016) and cardiovascular risks (Tobaldini et al., 2017). Additionally, healthy sleep has been observed to promote the formation of immunological memory thus enhancing immune function (Besedovsky, Lange, & Born, 2012). This is proposed to relate to enhanced levels of growth hormone and prolactin and reduced stress hormone cortisol during SWS (Besedovsky et al., 2012).

Sleep's importance on brain health and function has drawn intense focus. One of the most influential findings concerns the glymphatic system that serves waste disposal in the brain. That is, astroglial cells form perivascular channels that promote the removal of metabolic waste, thus mitigating the aggregation of proteins often linked with neurodegenerative disorders (Jessen, Munk, Lundgaard, & Nedergaard, 2015). Sleep characteristics are also associated with mental wellbeing such that less problems are found in those with healthy sleep (Kaneita et al., 2007; Wickham, Amarasekara, Bartonicek, & Conner, 2020; J. Zhang et al., 2017). Interestingly, there appears to be a bidirectional relationship between disordered sleep and psychopathology: psychiatric conditions may both lead to and result from impaired sleep (Lancel, Boersma, & Kamphuis, 2021). The causal path from sleep disturbance to psychopathology assumedly involves the dysfunction of hypothalamus-pituitary-adrenal axis (van Dalfsen & Markus, 2018) and disrupted emotional regulation by REM sleep (Pesonen et al., 2019a; Riemann, Krone, Wulff, & Nissen, 2020; Wassing et al., 2019).

Besides long-term implications on health, also day-to-day cognitive function is influenced by sleep. Performing daily activities requires attending

to relevant cues, planning, organizing and executing tasks, inhibiting adverse impulses and memorizing information that is salient for future goals. Studies where sleep is experimentally deprived or disrupted show adverse implications on tests of processing speed (Cohen-Zion, Shabi, Levy, Glasner, & Wiener, 2016), sustained attention (Hudson, Van Dongen, & Honn, 2020), task switching (Couyoumdjian et al., 2010) and working memory (Frenda & Fenn, 2016; Gerhardsson et al., 2019). In fact, sleep loss leads to hypoactivity in brain regions related to executive function, resembling the neural signature found in attention deficit and hyperactivity disorder (Saletin, Jackvony, Rodriguez, & Dickstein, 2019). Moreover, the ability to inhibit a response becomes impaired when sleep is deprived (Anderson & Platten, 2011; Demos et al., 2016). Research suggests that poor sleep may lead to increased risk-taking behavior (Killgore, 2015; Owens, Wang, Lewin, Skora, & Baylor, 2017; Womack, Hook, Reyna, & Ramos, 2013).

One domain perhaps most solidly associated with sleep is the formation of long-term memories. Indeed, the ability of brain to preserve and consolidate recently encountered information is strongly sleep-dependent (Rasch & Born, 2013), and the underlying processes and mechanisms are increasingly understood. The Chapter 2.3 addresses the topic in detail. First, what is meant by learning and memory?

## 2.2 LEARNING AND MEMORY

Stored information and memories of past experiences guide forthcoming choices in order to steer a creature towards survival and success. This behavioral adaptation is called learning. The term 'memory' refers to the construct of processes that enable learning (Kandel, Koester, Mack, & Siegelbaum, 2021). Indeed, memory is served by a multitude of partially distinct but interacting neurobehavioral cascades that are traditionally classified by the span of retention or by the nature of the memorized material or activity.

A widely adopted classification divides memory systems and processes by the duration and type of memories (Camina & Güell, 2017). Short- and long-term memory (STM and LTM, respectively) represent different conceptual systems where memories last only for a moment (STM), or for hours, weeks or even years (LTM). Long-term memories can be typified into declarative and non-declarative memories (Camina & Güell, 2017). The former refers to stored information that can be consciously recollected. Declarative memory consists of semantic knowledge (learned facts, meanings, context-independent) and episodic memories (experiences, autobiographical events, context-dependent). Non-declarative memories include skills and habits (i.e. procedural memories), conditioned responses, and habituation.

This thesis focuses particularly on declarative LTM. LTM consists of successive phases where information is encoded, consolidated and retrieved (Kandel et al., 2021). The following chapters address these phases in terms of the involved neural activity patterns and synaptic events.

### 2.2.1 THE ENCODING OF MEMORIES

Memory encoding is the process where incoming information gets processed in the way that enables subsequent storage (Davachi & Dobbins, 2008). Perhaps the most elemental anatomical structure in successful LTM encoding is the medial temporal lobe (MTL) (Kandel et al., 2021). Hippocampus within MTL is responsible for the formation of new episodic memories (Squire & Zola-Morgan, 1991). When experiencing an episode, like seeing new faces or listening to instructions, the incoming information is processed by separate components that are hosted by different brain areas. Hippocampus presumably binds these components such that they form an episodic memory (Nadel & Moscovitch, 1997). Conversely, hippocampal lesions result in inability to form new long-term memories even though STM would remain intact (Cave & Squire, 1992).

Forgetting events that are poorly attended is an easily recognizable everyday experience. Cognitive control processes that direct attention to task-/goal-relevant information support successful LTM formation (Blumenfeld & Ranganath, 2007). This top-down modulation is largely attributed to the prefrontal cortex (PFC), whose activation during LTM encoding is well-documented (Blumenfeld & Ranganath, 2007; Buckner, Kelley, & Petersen, 1999) and is facilitated by bidirectional projections between PFC and MTL (Preston & Eichenbaum, 2013). Evidence from reward-seeking rodents indicates that coherent firing between prefrontal and hippocampal cell assemblies determines which information is stored in LTM (Benchenane et al., 2010). Such 'tagging' is proposed to be important in subsequent consolidation, especially during sleep (Squire, Genzel, Wixted, & Morris, 2015).

Behavioral studies show that memory performance tends to be better for emotional information than neutral (Kensinger, 2009; Talmi, 2013). Accordingly, amygdala activation – a neural hallmark of emotional processing (Phelps & LeDoux, 2005; Sergerie, Chochol, & Armony, 2008) – during encoding correlates with better retention of emotional items (Kensinger, Addis, & Atapattu, 2011; Kensinger & Schacter, 2006; Phelps, 2004). A major factor contributing to these observations is how emotion modulates the strength of encoding. In part this relates to bottom-up perceptual enhancement of provocative stimuli (Mather & Sutherland, 2011), thus promoting encoding success. However, emotional arousal appears to influence

memory processing beyond attentional capture. It has been proposed that amygdala activity during encoding modulates structures involved in memory formation, mainly hippocampus (Bergado, Lucas, & Richter-Levin, 2011; Lynch, 2004).

The cellular conceptualization of the formation of long-term memories leans heavily on activity-dependent changes in synaptic efficacy. The concept dates decades back to Donald Hebb (Hebb, 1949) who postulated that synaptic strength was increased if the concerned neurons were simultaneously active. The prevalent model for the underlying mechanism is long-term potentiation (LTP), where the synchronous activity of pre- and postsynaptic neurons facilitate a strong calcium influx in the postsynaptic neuron's dendritic spines (Schiller, Schiller, & Clapham, 1998). The calcium influx results from the activation of both voltage-dependent calcium channels and the N-Methyl-D-aspartate type glutamate receptors (NMDAR) (Schiller et al., 1998). The opposing process, long-term depression (LTD), results from a lower-amplitude calcium surge and leads to the weakening of synaptic connections (Artola & Singer, 1993). While these events of synaptic plasticity were initially investigated in hippocampal neurons (Bliss & Collingridge, 1993), later work has shown their relevance in structures like neocortex (Kirkwood, Dudek, Gold, Aizenman, & Bear, 1993) and amygdala (Maren, 1999).

### 2.2.2 MEMORY CONSOLIDATION

The persistence of a new potentiation involves two types of consolidation: synaptic and systems consolidation (Dudai, 2004). The former refers to a process where early-phase LTP (E-LTP), a potentiation which decays within a few hours, is transformed to a persisting potentiation, i.e. late-phase LTP (L-LTP) (Bramham & Messaoudi, 2005). Whereas E-LTP is underlain by temporary enhancement in cellular calcium dynamics (Lisman, Yasuda, & Raghavachari, 2012), L-LTP requires new protein synthesis (Bramham & Messaoudi, 2005). The division to these non-persisting and stabilized forms of LTP begs the question which mechanism evokes the persistence, analogous to an every-day situation where one thing is forgotten and another is not. A line of evidence supports 'synaptic tagging', where tagged synapses capture proteins needed for L-LTP (Frey & Morris, 1997; Redondo & Morris, 2011). The tag in the concerned synapses is presumed to be set by intense stimulation. This parallels, at the behavioral level, memory encoding with goal-driven (Blumenfeld & Ranganath, 2007) or amygdalar (Bergado et al., 2011) modulation.

Systems consolidation, on the other hand, refers to a process where novel hippocampal-dependent memories become redistributed into cortical representations (Frankland & Bontempi, 2005; Squire et al., 2015; Takashima

et al., 2009). This redistribution presumably involves recurrent memory reactivations and waves of synaptic consolidation that take place in the concerned neuronal circuits (Dudai, Karni, & Born, 2015; Frankland & Bontempi, 2005). While the time course required for this redistribution may vary from hours to years (Dudai et al., 2015), one factor is considered essential for the process: sleep. Indeed, depriving sleep after memory encoding may irreversibly disturb systems consolidation. This has been demonstrated, for example, in humans with differential cortical activation patterns between two groups, one group with post-encoding sleep and the other deprived from it (Gais et al., 2007).

### 2.2.3 RETRIEVING MEMORIES

Information stored in the LTM can be later retrieved via different strategies. Recognition refers to a process where the presentation of a previously memorized stimulus causes a sense of familiarity or a recollection of the situation where the stimulus was previously encountered (Brown & Aggleton, 2001). Whereas recognition postulates the presentation of a previously encoded stimulus, *free recall* refers to active retrieval of studied items without an enhancement of explicit cues (Higham & Guzel, 2012). In *cued recall*, instead, retrieval is aided with a cue that has been connected (e.g. temporally or semantically) to the to-be-retrieved information (Higham & Guzel, 2012).

Brain regions commonly associated with the retrieval of declarative memories comprise medial temporal lobe (Preston & Eichenbaum, 2013; Rugg & Vilberg, 2013), PFC (Preston & Eichenbaum, 2013) and – in case of emotional memories – amygdala (Buchanan, 2007). The extent of contextual information and details retrieved appears to correlate with the recruitment of especially hippocampus (Frankland & Bontempi, 2005). That is, if the retrieved information is accompanied by details representing the study episode (i.e. 'recollection'), the binding process that forms an integrated memory is considered to rely on hippocampus (Rugg & Vilberg, 2013). 'Familiarity' type of retrieval may, instead, utilize partially different MTL structures, such as perirhinal cortex (Rugg & Vilberg, 2013). Finally, the relative recruitment between hippocampal and neocortical structures during memory retrieval depends on the stage of systems consolidation. That is, novel memories are dependent on hippocampally-centered activity, whereas consolidation results in elevated neocortical activity and connectivity (Frankland & Bontempi, 2005; Takashima et al., 2009).

Taken together, declarative LTM is served by the interplay between MTL structures and neocortical areas. A body of research underlines the importance of the interactive facilitation of especially hippocampus and PFC during the

formation, consolidation and retrieval of LTMs. At the cellular level, activity-dependent differences in synaptic weights, induced chiefly by LTP and LTD, are largely considered the neurophysiological basis of memories. After successfully elicited by strong stimulation, the weight differences may get consolidated into enduring engrams. The most elemental factor in this process is sleep.

## 2.3 SLEEP AND MEMORY

Abundance of research advocates for sleep's benefit on memory (Rasch & Born, 2013): memory retention over a sleep-containing period is generally better compared to remaining awake. This phenomenon has been explained by three roles of sleep in memory retention: passive, permissive and active (Ellenbogen, Payne, & Stickgold, 2006). According to the *passive* hypothesis, sleep merely shelters recent memories from waking mental activity that would interfere with the memories. Thus, during sleep, memories remain unchanged. Any sleep-over-wake retention benefits relate to reduced forgetting, rather than any sleep-dependent consolidative process. *Permissive* hypothesis also recognizes the reduced interference. However, it goes beyond passive sheltering to assume that certain brain activity that is already in place during waking get an enhanced opportunity for memory consolidation during sleep. Thus, sleep serves memory indirectly without necessarily offering any unique contribution. Finally, *active* hypothesis postulates that sleep has specific properties that directly support the consolidation of recent memories. This active role gained momentum from early studies applying a half-night paradigm, as it was observed that SWS and REM sleep seemed to contribute differentially on post-sleep memory outcome (Barrett & Ekstrand, 1972; Fowler, Sullivan, & Ekstrand, 1973). Studying sleep with electroencephalography (EEG) has identified neural patterns and microstructural events (e.g. sleep spindles) that are believed to be causally linked with active memory consolidation (Born & Wilhelm, 2012). Additionally, efforts have been made to reactivate conditioned memories by sensory stimuli during sleep. This targeted memory reactivation has been shown to enhance memory outcome (Lewis & Bendor, 2019), supporting the active role of sleep in memory consolidation.

Recent research on sleep and memory rarely contrasts these roles. Rather, each may carry relevance that depend on factors like the type of the memory task and its timing relative to sleep, and disentangling the contribution of these roles would likely prove challenging. However, research focus is increasingly gravitating toward active consolidation mechanisms that enable causal understanding behind the phenomenon.

### 2.3.1 SLEEP, ITS TIMING AND MACROSTRUCTURE

The elementary approach regarding sleep's benefit on learning is to question whether memory retention is better over a sleep-containing period, relative to remaining awake. An agreement is reached by several studies in different domains of declarative LTM, such as picture recognition (Baran, Pace-Schott, Ericson, & Spencer, 2012), verbal associations (Ellenbogen, Hulbert, Jiang, & Stickgold, 2009; Potkin & Bunney, 2012), face recognition (Sheth, Nguyen, & Janvelyan, 2009) and face-name associations (Maurer et al., 2015). The timing of the post-encoding sleep may be relevant, too. Sleep-related performance benefits are reportedly greater when the delay between learning and sleep is short, compared to staying awake for a longer time (Gais, Lucas, & Born, 2006; Talamini, Nieuwenhuis, Takashima, & Jensen, 2008; Wagner, Kashyap, Diekelmann, & Born, 2007). These findings align well with the accounts how (prolonged) wake can impair memory. First, labile memory traces are exposed to non-specific interference by any mental activity (Wixted, 2004). Second, remaining awake builds up sleep pressure and decreases the signal-to-noise ratio of potentiated synapses (Tononi & Cirelli, 2014).

The impact of sleep on memory retention goes beyond the passive role of replacing wake. Even short periods of post-encoding sleep suffice to benefit learning (Lahl, Wispel, Willigens, & Pietrowsky, 2008; Tucker & Fishbein, 2009), and sleep-consolidated memories may stand strong against subsequent interference (Alger, Lau, & Fishbein, 2012; Sheth, Varghese, & Truong, 2012). Sleep consists of different stages that may contribute dissimilarly to learning, depending on the type of learning. According to a rather traditional view, i.e. dual-process hypothesis, declarative memories are consolidated during SWS whereas implicit, procedural and emotional information benefit from REM sleep (Rasch & Born, 2013). The steepness of this dichotomy has since been contested by accounts indicating, for example, that SWS promotes procedural learning (Ackermann & Rasch, 2014). Moreover, NREM stage 2 appears to support both procedural (Boutin et al., 2018) and declarative learning (Ruch et al., 2012), which has been attributed to sleep spindles that are frequent during that stage (Fogel & Smith, 2006; Gais, Mölle, Helms, & Born, 2002). Furthermore, REM sleep theta activity associates with memory outcome in image recognition tasks (Nishida, Pearsall, Buckner, & Walker, 2009; Sopp, Michael, Weeß, & Mecklinger, 2017). Indeed, to understand how different sleep stages are involved in memory retention necessitates investigating their characteristic microstructural events.

### 2.3.2 SLEEP SPINDLES IN MEMORY CONSOLIDATION

A hallmark of NREM sleep (Andrillon et al., 2011), sleep spindles are short (~0.5–2 second) bursts of rhythmic thalamocortical oscillations in the frequency range of ~10–16 Hz (De Gennaro & Ferrara, 2003). Spindles are evoked by inhibitory bursts of GABAergic neurons in thalamic reticular nucleus (TRN) causing postinhibitory rebounds in thalamocortical cells (De Gennaro & Ferrara, 2003). The excitatory post-synaptic potentials re-excite TRN neurons, which generates a repetitive, synchronized excitatory-inhibitory cycle (Clawson, Durkin, & Aton, 2016; De Gennaro & Ferrara, 2003). This oscillatory burst, i.e. sleep spindle, is transferred to cortical areas via thalamocortical axons and then further amplified by intra-cortical projections (Lüthi, 2014). White matter tracts are essential for efficient propagation of sleep spindles, and their diffusion metrics have been shown to associate with spindle properties (Gaudreault et al., 2018; Piantoni et al., 2013).

Sleep spindles are generally divided into two subtypes based on their internal frequency. Slow spindles (< ~13 Hz) usually occupy anterior areas of the brain whereas fast spindles are predominant in centro-parietal regions (De Gennaro & Ferrara, 2003). However, no fine-cut distinction can be made between slow and fast spindles as the frequency change proceeds rather gradually between parietal and frontal areas (Peter-Derex, Comte, Mauguière, & Salin, 2012), and both spindle types do occur in their non-preferred areas (Sopp et al., 2017). Moreover, it remains unclear whether distinct thalamic generators underlie fast and slow spindles (Fernandez & Lüthi, 2020).

Sleep spindles are an acknowledged biomarker of memory processing during sleep. Evidence from behavioral studies in humans indicates that spindle activity during memory retention associates with better performance in different types of declarative (Clemens, Fabo, & Halasz, 2006; Clemens, Fabó, & Halász, 2005; Gais et al., 2002; Genzel, Dresler, Wehrle, Grözinger, & Steiger, 2009; Nishida & Walker, 2007; Ruch et al., 2012; van der Helm, Gujar, Nishida, & Walker, 2011) and procedural (Barakat et al., 2013; Boutin et al., 2018; Fogel & Smith, 2006; Laventure et al., 2016) learning. On the other hand, learning also elevates spindle activity during the subsequent sleep (Fogel & Smith, 2006; Gais et al., 2002; Morin et al., 2008; Peters, Ray, Smith, & Smith, 2008; Schmidt et al., 2006). The memory function of spindles can be elucidated by considering synaptic plasticity. During spindles, NMDAR activation triggers strong $Ca^{2+}$ influx that leads to postsynaptic signaling cascades underlying LTP (Lindemann, Ahlbeck, Bitzenhofer, & Hanganu-Opatz, 2016). Accordingly, it has been demonstrated in vitro that a spiking pattern that resembles sleep spindles results in $Ca^{2+}$ channel-dependent LTP (Rosanova & Ulrich, 2005). In addition to being involved in synaptic plasticity, sleep spindles facilitate systems consolidation, i.e. the process where labile,

hippocampus-dependent memory traces are transferred to long-term neocortical representations (Klinzing, Niethard, & Born, 2019). Functional connectivity between hippocampus and neocortex is elevated during sleep spindles (Andrade et al., 2011). Indeed, such 'dialogue' is shown to play a causal role in memory consolidation during sleep (Maingret, Girardeau, Todorova, Goutierre, & Zugaro, 2016). Concerning spindle type (i.e. fast and slow spindles), primarily fast spindles are considered to benefit memory consolidation (Mölle, Bergmann, Marshall, & Born, 2011). This is attributed to elevated hippocampal activity during fast spindles (Schabus et al., 2007) and different alignment on slow oscillation: fast spindles tend to peak during the depolarized SO upstate, whereas slow spindles accumulate after the positive-to-negative transitions (Muehlroth et al., 2019; Mölle et al., 2011).

### 2.3.3 THE COUPLING OF SPINDLES AND SLOW OSCILLATIONS

Inspecting sleep spindles in isolation is insufficient in terms of both synaptic plasticity and systems consolidation. Sleep spindles are intensely bound with other NREM sleep oscillations, especially neocortical slow oscillations (SO) (Staresina et al., 2015). SOs are generated when large cortical populations undergo slow (~0.2–1.25 Hz), repeating, synchronized transitions between high synaptic activity and silence (Neske, 2015). During the active, depolarized period (i.e. 'upstate'), synapses are biased towards potentiation (Chauvette, Seigneur, & Timofeev, 2012), whereas hyperpolarized 'downstates' are considered cellular rest (Vyazovskiy & Harris, 2013). When the wide depolarization reaches TRN via cortico-thalamic pathways, it may trigger a spindle that traverses to cortex via thalamocortical projections (Steriade, 2006). A spindle that co-occurs with the depolarized SO upstate provides a prominent window for memory consolidation (Klinzing et al., 2019). Accordingly, behavioral studies in humans have shown that the timing constancy of SO–spindle coupling associates with learning over sleep (Hahn, Heib, Schabus, Hoedlmoser, & Helfrich, 2020; Helfrich, Mander, Jagust, Knight, & Walker, 2018; Mikutta et al., 2019; Muehlroth et al., 2019). It is of note that pre-sleep learning also augments SO-upstate-coupled spindle activity (Mölle, Eschenko, Gais, Sara, & Born, 2009; Yordanova, Kirov, Verleger, & Kolev, 2017), indicating that coupling properties are partially dynamic and derive from wake-time activation.

The sources of inter-individual variability in SO-spindle coupling properties are rather scarcely explored, but one obvious correlate is age. During adolescence, sleep spindle characteristics undergo several changes, including increasing frequency and density peaking around the age of 15 (Z. Y. Zhang, Campbell, Dhayagude, Espino, & Feinberg, 2021). In addition, slow oscillation onset becomes more anterior (Timofeev et al., 2020). The strength of SO-spindle coupling increases between childhood and middle adolescence,

this maturational change predicting memory consolidation improvement (Hahn et al., 2020). Old age, on the other hand, is featured by the dispersion of SO-spindle coupling, which associates with impaired memory consolidation (Helfrich et al., 2018; Muehlroth et al., 2019). This decline has been attributed to integrity loss in source regions of SOs and spindles, such as medial PFC (Helfrich et al., 2018; Muehlroth et al., 2019).

Arguably, SOs and sleep spindles have an auxiliary role in memory consolidation, as they cannot access the hippocampal memory engram (Langille, 2019). Instead, hippocampal sharp-wave ripples (SWR), high-frequency (~80–140 Hz in humans (Le Van Quyen et al., 2008)) oscillations, are considered to represent the offline reactivation of those neuronal sequences that were active during the recent learning (Atherton, Dupret, & Mellor, 2015; Buzsáki, 2015). In isolation, however, SWRs can lead to the depression of hippocampal synapses (Norimoto et al., 2018), and cortical memory trace is not consolidated (Peyrache & Seibt, 2020). A spindle, in combination with the memory reactivation by SWR, induces synaptic plasticity, thus facilitating the consolidation of the memory (Peyrache & Seibt, 2020). In addition, the synchronized events of SO-coupled spindles are found to trigger SWRs (Helfrich et al., 2019), thus actively being involved in sleep-dependent consolidation and providing a powerful correlate of post-sleep memory performance (Hahn et al., 2020; Helfrich et al., 2018; Mikutta et al., 2019; Muehlroth et al., 2019).

The assumption that SO-coupled spindles provide mechanistic means for memory consolidation leads to a methodological issue in majority of human studies investigating the topic. Namely, the synchrony is mainly examined using relative values, that is, the *tendency* for positive SO-peak proximity. Such values include resultant vector length (Helfrich et al., 2018), non-event tied phase-amplitude coupling (Mikutta et al., 2019) mean circular distance between spindles and the positive SO peak (Hahn et al., 2020), mean SO angle of spindle peaks (Mikutta et al., 2019) or a proportional amount of SO-coupled spindles (Denis et al., 2020). The relative measures of SO-coupled spindles may be equal even if the raw number of these events is not, even though the assumed effect of synaptic strengthening would possibly be better captured by the amount of these events. Actually, it is plausible that factors influencing the timing characteristics of SO-coupled spindles, such as prefrontal-MTL structural integrity (Muehlroth et al., 2019), could also affect on memory functioning. In that case, precise SO-spindle synchrony would rather be an indicator of, than causally drive, efficient memory consolidation.

The evident significance of the SO-spindle-SWR coordination on memory consolidation begs the question why several studies report associations between declarative memory and specifically N2 spindles (Gais et al., 2002; Genzel et al., 2009; Göder et al., 2015; Ruch et al., 2012; van der

Helm et al., 2011), even though spindle-related benefits on memory are proposed SWS-dependent due to abundant SOs during the stage (Cox, Hofman, & Talamini, 2012). One possibility is that N2 spindles indicate general learning aptitude or fluid cognitive skills (Fang et al., 2017; Schabus et al., 2006), whereby associations with learning would be a byproduct of neural efficiency (Fogel & Smith, 2011; Lustenberger, Maric, Dürr, Achermann, & Huber, 2012), rather than causally serving memory consolidation. However, N2 spindles may well be involved in hippocampal-neocortical dialogue, supported by elevated functional connectivity within that network during specifically N2 spindles (Andrade et al., 2011). Additionally, it has been proposed that the memory benefits by N2 spindles would rely on similar mechanisms as N3 spindles, because large depolarizations in the form of K-complexes are frequent during N2 (Ruch et al., 2012).

### 2.3.4 INTER-SPINDLE SYNCHRONY

It is frequently observed that sleep spindles in separate cortical locations tend to overlap temporally (Frauscher et al., 2015; O'Reilly & Nielsen, 2014; Piantoni, Halgren, & Cash, 2017; Souza, Gerhardt, Schönwald, Rybarczyk-Filho, & Lemke, 2016). Such a widespread, synchronized spindling is proposed to reflect a thalamocortical "matrix" pathway, differing from the "core" pathway (local spindles) in terms of involved thalamic nuclei and projected cortical layers (Bonjean et al., 2012; Piantoni, Halgren, & Cash, 2016). Different studies have characterized these global spindles by e.g. their propagation velocity or preferred direction (Frauscher et al., 2015; O'Reilly & Nielsen, 2014; Piantoni et al., 2017; Souza et al., 2016). While methodological differences hinder the generalizability between these studies, one interesting finding is the rapid phase synchronization between overlapping spindles (Souza et al., 2016). Evidence from waking brains indicate that coherent firing between distinct brain areas marks efficient communication (Fell & Axmacher, 2011) and is associated with performance in tasks of working memory (J. M. Palva, Monto, Kulashekhar, & Palva, 2010; S. Palva, Monto, & Palva, 2010; Schack & Weiss, 2005), executive function (Mizuhara & Yamaguchi, 2007; Sadaghiani et al., 2012) and delayed recognition memory (Rutishauser, Ross, Mamelak, & Schuman, 2010). Remarkably, one study found learning-related increases in inter-electrode EEG coherence during post-learning sleep in several frequency bands, including spindle range (Mölle, Marshall, Gais, & Born, 2004). The authors speculated that the increase in the coherence between distinct cell assemblies would reflect the neural activity during encoding, then orchestrated by thalamocortical connections during sleep. These findings make it intriguing to ask whether the synchronization properties of propagated spindle events have specific implications for long-term memory retention. Beyond a speculated role in the processing of

widespread memory representations (Piantoni et al., 2016), no study thus far has addressed the issue.

### 2.3.5 SYNAPTIC HOMEOSTASIS HYPOTHESIS

Interacting with the environment during waking induces a continuous flow of information that is variably attended and processed. This activity is facilitated by neuronal firing, which potentiates synaptic connections in order to learn statistical regularities about the environment (Tononi & Cirelli, 2014). Increased synaptic strength comes at the cost of elevated need for energy and supplies. Additionally, learning gets saturated and relative differences in synaptic weights decrease.

"Sleep is the price the brain pays for plasticity", states the synaptic homeostasis hypothesis (SHY) (Tononi & Cirelli, 2014). Indeed, plasticity is requisite for survival and SHY posits that sleep covers the cost of excess potentiation. This has been proposed to result from global downscaling where synaptic strengths, elevated due to waking experiences, are renormalized to the homeostatic ranges. This downscaling is largely attributed to cortical slow-wave activity (SWA), i.e. slow (0.5–4 Hz) coherent firing of large neuronal populations, that is especially rich during the early part of nocturnal sleep and decreasing towards morning (Vyazovskiy et al., 2009). SWA is considered to indicate widespread synaptic potentiation (Huber et al., 2007) and, accordingly, the need of sleep (Dijk, 2009). The cellular basis for the SWA-tied downscaling includes the depression of postsynaptic potentials (Czarnecki, Birtoli, & Ulrich, 2007) and reduction of AMPA receptors (Diering et al., 2017; Lanté, Toledo-Salas, Ondrejcak, Rowan, & Ulrich, 2011). A complementary view on SWA-induced cortical downscaling concerns REM sleep and the depotentiation of hippocampal synapses, as theta activity during REM sleep has been observed to decrease hippocampal firing rates (Grosmark, Mizuseki, Pastalkova, Diba, & Buzsáki, 2012). The importance of downscaling for subsequent learning has been modeled by demonstrating that the dissipation of SWA improved signal-to-noise ratios and desaturated the learning ability (Olcese, Esser, & Tononi, 2010). In humans, prolonged wake impairs LTP-like plasticity, which is presumably mediated by reduced brain-derived neurotropic factor (BDNF) along sleep deprivation (Kuhn et al., 2016). Moreover, experimentally manipulating SWA has been associated with the encoding capacity (Antonenko, Diekelmann, Olsen, Born, & Mölle, 2013; Van Der Werf et al., 2009).

Besides restoring encoding capacity, SHY also models the preservation of novel memories. However, complete downscaling of the potentiation caused by wake-time activity would prevent long-term learning. SHY counters this by assuming that sleep-related downscaling maintains the relative differences in

synaptic weights, thus preserving the representations of strongly encoded events (i.e. memories). This result has been computationally modeled using different logics, such as equal downscaling of all synapses, where the weakest ones are reduced to below firing threshold (Hill, Tononi, & Ghilardi, 2008); with less depression of strong, compared to weak, synapses (Olcese et al., 2010); or with the protection of strongly activated synapses (Hashmi, Nere, & Tononi, 2013). The assumed synapse-specificity counters arguments that have arisen due to several deviations from the global nature of the downscaling (Puentes-Mestril & Aton, 2017). Indeed, later work advocates for down-selection, instead of global downscaling (Tononi & Cirelli, 2020). The down-selection hypothesis has found support in *in vivo* experiments. It was reported that synapses are biased toward depression during SO upstates, save for coincidently firing pre- and postsynaptic pairings, i.e. synapses with highest weights (González-Rueda, Pedrosa, Feord, Clopath, & Paulsen, 2018). Furthermore, a study with mice showed that neurons that were active during pre-sleep exploration kept reactivating during sleep SWRs, thus protecting certain synapses from downscaling that occurred in memory-irrelevant synapses (Norimoto et al., 2018). In sum, while the major component of SHY on memory function relates to synaptic downscaling, similarities with active consolidation are perceivable. That is, neural activity during wake selectively modulates sleep-related firing that maintains or potentiates relevant memories.

### 2.3.6 IS MEMORY CONSOLIDATION OVER SLEEP SELECTIVE?

A line of research proposes that sleep preferentially consolidates memories that are salient for future (S. Y. Kim & Payne, 2020). Indeed, preserving the information that may promote survival makes evolutional sense, whereas getting rid of non-relevant events and details sustains the ability for subsequent encoding. In experimental studies this saliency has been modulated by factors like task instructions (Saletin, Goldstein, & Walker, 2011), reward (Fischer & Born, 2009) or the expectancy of future retrieval (Wilhelm et al., 2011). Importantly, the emotional arousal caused by an event or item represents an evolutionally preserved mechanism for marking information that is relevant for success and survival (Tyng, Amin, Saad, & Malik, 2017). Accordingly, sleep is believed to consolidate emotional memories in elevated efficacy, relative to neutral ones (S. Y. Kim & Payne, 2020). As previously noted, the encoding of emotional information is speculated to set a tag for subsequent consolidation (Bergado et al., 2011). During sleep, these memories get selectively consolidated (S. Y. Kim & Payne, 2020) whereas unnecessary synaptic connections are downscaled according to synaptic homeostasis hypothesis (Tononi & Cirelli, 2014). Sleep oscillations during NREM sleep, such as spindles, are likely involved in this selective consolidation by repeatedly reactivating the related network (Seibt & Frank,

2019). Accordingly, sleep spindles are found to associate with selective consolidation by their role in either activating salient information (Kaestner, Wixted, & Mednick, 2013; Studte, Bridger, & Mecklinger, 2017) or inhibiting non-relevant aspects (Cairney, Durrant, Jackson, & Lewis, 2014).

Even though it makes intuitive sense that highly affective experiences should be better preserved, systematically comparing the selective benefits between sleep and wake does not cement the viewpoint. Drawing together the conclusions from two meta-analyses (Lipinska, Stuart, Thomas, Baldwin, & Bolinger, 2019; Schäfer et al., 2020) and one review (Davidson, Jönsson, Carlsson, & Pace-Schott, 2021), sleep appears not to boost memory performance for 'salient' – be it by top-down regulation (e.g. instructions) or via bottom-up emotional processes – memories more stronger than is observed over wake condition. That is, while salient memories are usually better retrieved relative to non-salient ones, this preference does not depend on the type of the delay (sleep / wake). However, it is possible that a subtle phenomenon could get obscured by methodological variation in factors like task type and difficulty (Lipinska et al., 2019). Moreover, studies focusing on a specific sleep stage such as REM sleep (Schäfer et al., 2020) appear more potent in perceiving saliency-preference. Along the same vein, specific NREM mechanisms like sleep spindles (Alger, Chen, & Payne, 2019; Cairney et al., 2014; Kaestner et al., 2013; Wilhelm et al., 2011) or their coupling with SOs (Denis et al., 2020) may capture dynamics that gets lost by operationalizing sleep as a binary condition or by its duration only.

A completely different perspective on material-based selectivity concerns the difficulty of encoded items. In the context of verbal LTM, the difficulty can be understood by the semantic relatedness of e.g. word-pairs: 'fire – smoke' representing relatedness and 'fire – clown' unrelatedness (Payne et al., 2012b). It appears that sleep serves especially the retention of unrelated word-pairs (Payne et al., 2012b). This aligns with findings where sleep-related benefits are emphasized in the case of difficult encoding, manipulated by the word-pair abstractness/concreteness (Schmidt et al., 2006), or by the number of encoding rounds (Denis et al., 2021). Remarkably, in these latter studies, sleep spindles were identified as the facilitators of this selective consolidation process.

### 2.3.7 REM SLEEP OSCILLATIONS AND MEMORY

Even though this thesis mainly focuses on NREM oscillations attributed to declarative memory consolidation, a brief overview on REM oscillations is in order. As brought up earlier, REM sleep is generally linked with different forms of procedural learning. However, its contribution on declarative memory concerns especially emotional memories. This is attributed to theta

wave (~4–8 Hz) activity, which is believed to represent the synchronized activity between amygdala and hippocampus, thus promoting emotional memory processing (Hutchison & Rathore, 2015). Behavioral experiments in humans have shown right-dominant prefrontal REM sleep theta to associate with the retention of emotional information over sleep (Nishida et al., 2009; Sopp et al., 2017). Additionally, REM sleep is associated with a neurochemical milieu with high acetylcholine and low noradrenaline levels. Theta activity in such state presumably enables the integration and recombination of novel memory traces into existing representations (Hutchison & Rathore, 2015). This adheres to the 'sequential hypothesis', according to which the memories that have been systems-consolidated during NREM sleep are integrated to pre-existing memories during the subsequent REM period (Sterpenich et al., 2014).

## 2.4 PLASTICITY GENES

The emergence of neurogenetics has enabled compelling possibilities to investigate heritable factors in cognitive function. In overnight learning, of specific relevance are genes that have been linked with the development and function of hippocampal and prefrontal areas, due to their documented role in mnemonic functions. These include (while not limited to) the genes encoding brain-derived neurotrophic factor (*BDNF*) and catechol-O-methyltransferase (*COMT*).

### 2.4.1 BRAIN-DERIVED NEUROTROPHIC FACTOR

Brain-derived neurotrophic factor (BDNF) belongs to the neurotrophin family, regulating neurons' survival, development, and function (Zagrebelsky & Korte, 2014). The influence of BDNF on synaptic plasticity is manifold and is mainly promoted by its binding to tropomyosin related kinase B (TrkB) receptors (Sandhya et al., 2013). BDNF promotes the induction, expression and maintenance of LTP, whereas it also blocks long-term depression (LTD) (Bramham & Messaoudi, 2005; Poo, 2001). On one hand, BDNF influences intracellular calcium concentration via regulating the trafficking (Caldeira et al., 2007) and phosphorylation (Lin et al., 1998) of NMDARs. Furthermore, BDNF promotes the formation of late-phase LTP, i.e. potentiation lasting longer than 1-2 hours: BDNF-TrkB signaling stimulates dendritic protein synthesis that facilitates persistent synaptic strengthening (Panja & Bramham, 2014) and induces LTP-related cytoskeletal changes (Rex et al., 2007). Interestingly, in the light of the synaptic tagging and capture hypothesis (Frey & Morris, 1997; Redondo & Morris, 2011), activated TrkB receptors have been proposed as synaptic tags and BDNF the captured protein that would establish L-LTP (Lu et al., 2011).

BDNF is encoded by the gene *BDNF*. A single nucleotide polymorphism in *BDNF* gene that has drawn interest in human memory research is Val66Met, where valine (Val) is replaced with methionine (Met) in the codon 66. Val66Met is associated with impaired intracellular trafficking and reduced activity-dependent secretion of BDNF (Z.-Y. Chen et al., 2004). In humans, the polymorphism is linked with neurostructural and -functional implications: the carriers of $Met_{BDNF}$ allele(s) show reduced volume in hippocampal areas (Montag, Weber, Fliessbach, Elger, & Reuter, 2009; Pezawas et al., 2004), PFC (S. N. Kim et al., 2013; Pezawas et al., 2004) and amygdala (Molendijk et al., 2012; Montag et al., 2009) and altered activation of these areas during executive (Schofield et al., 2009) and mnemonic (Egan et al., 2003; Molendijk et al., 2012) tasks. Imaging studies targeting the structural integrity of white matter tracts have instead shown higher anatomical connectivity along $Met_{BDNF}$ alleles (Carlson, Cha, Harmon-Jones, Mujica-Parodi, & Hajcak, 2014; Chiang et al., 2011; Tost et al., 2013; Ziegler et al., 2013). However, one study showed that Val66Met-related differences in gray or white matter properties are not invariably detected (McKay, Moreau, Henare, & Kirk, 2019).

The Val66Met-related influences on functional and anatomical correlates of memory has motivated examining behavioral consequences of the polymorphism. Spearheaded by the hypothesis-concordant observations of $Val_{BDNF}$ homozygotes outperforming $Met_{BDNF}$ carriers in memory tasks (Egan et al., 2003), the topic has been since examined extensively. While not reaching a complete consensus, a systematic review on Val66Met and cognitive function indicated mnemonic advantage via $Val_{BDNF}$ homozygosity in 30.2 % of the scrutinized studies, compared to 11.1 % for $Met_{BDNF}$ carriers (Toh, Ng, Tan, Tan, & Chan, 2018). It is of note that few studies have examined how sleep interacts with Val66Met on memory outcome. One study administering post-sleep memory tasks found that non-fragmented sleep associated with better performance in $Val_{BDNF}$ homozygotes, the relation was opposite in $Met_{BDNF}$ carriers (Gosselin et al., 2016). While the retention did not contain sleep, the result suggests that $Val_{BDNF}$ homozygotes, relative to $Met_{BDNF}$ carriers, are more dependent on sleep quality in terms of efficient mnemonic functions. Studies investigating how Val66Met and sleep interact during the retention period indicate either no overall memory outcome difference (Harrington et al., 2019) or a sleep-related benefit for $Val_{BDNF}$ homozygotes (Cathomas, Vogler, Euler-Sigmund, de Quervain, & Papassotiropoulos, 2010; Mascetti et al., 2013). One of these latter studies associated slow oscillation power with memory processing in $Val_{BDNF}$ homozygotes only (Mascetti et al., 2013). This implies that mechanisms of sleep-dependent memory consolidation are affected by Val66Met, resulting on subsequent performance. However, whereas the interaction between Val66Met and sleep may not evoke overall differences in retention performance, some evidence exists that specifically emotional memories are

selectively preserved in $Met_{BDNF}$ carriers (Harrington et al., 2019) – at the expense of neutral ones?

Val66Met has drawn focus regarding sleep homeostasis as well. Given that BDNF expression during wakefulness predicts subsequent SWA (Faraguna, Vyazovskiy, Nelson, Tononi, & Cirelli, 2008; Huber et al., 2007), the indicator of homeostatic sleep pressure (Dijk, 2009), it is warranted to speculate that Val66Met would implicate the dynamics of sleep pressure in humans. One study deploying comprehensive spectral power analyses demonstrated that SWA builds up steeper in $Val_{BDNF}$ homozygotes relative to $Met_{BDNF}$ carriers (Bachmann et al., 2012). It also declines swiftly to equal the level of $Met_{BDNF}$ carriers early during night's sleep (Bachmann et al., 2012). In sum, $Val_{BDNF}$ homozygosity appears to associate with greater accumulation of sleep pressure towards sleep onset, this probably underlain by BDNF's effect on synaptic potentiation (Huber et al., 2007).

These findings point out research needs regarding the interplay between Val66Met, sleep and memory performance. First, current understanding is lacking regarding how Val66Met-related implications on sleep homeostasis would affect memory retention over a sleep-containing period. Sleep pressure is mediated by adenosine (Porkka-Heiskanen et al., 1997), and accumulated adenosine may inhibit synaptic transmission as well as the plasticity-inducing second messenger activity (Prince & Abel, 2013). Hence, the effects of prolonged wake could interact with the allelic composition of *BDNF* gene on memory. Second, Val66Met may interact with sleep-dependent consolidation mechanisms, primarily sleep spindles. Sleep spindles are featured with a strong calcium influx into neurons via NMDAR activation (Lindemann et al., 2016). BDNF enhances NMDAR activity (Caldeira et al., 2007), and thus carrying $Met_{BDNF}$ alleles may limit NMDAR-dependent plasticity (Ninan et al., 2010). Conversely, sleep spindle bursts have been proposed a physiological trigger for BDNF release (Yang, Reyes-Puerta, Kilb, & Luhmann, 2016).

### 2.4.2 CATECHOL-O-METHYLTRANSFERASE

Dopamine is a neurotransmitter whose prefrontal activity is found to influence multiple aspects of goal-driven behavior (Ott & Nieder, 2019) and it also drives synaptic plasticity via the activation of ERK1/2 pathway (Otani, Daniel, Roisin, & Crepel, 2003). The degradation, and thus, availability of dopamine in the PFC is regulated by the enzyme catechol-o-methyltransferase (COMT) (J. Chen et al., 2004). The rate of dopamine metabolism in humans is associated with the *COMT* gene, where a substitution from methionine to valine allele (Val158Met) results in faster inactivation of extracellular dopamine in the PFC (J. Chen et al., 2004). Given the importance of prefrontal dopamine in tasks of cognitive control (Ott & Nieder, 2019), $Val_{COMT}$ allele is

expectedly related with impaired performance in tasks of executive function (Egan et al., 2001; Wishart et al., 2011) and working memory (Bruder et al., 2005). Interestingly, also decreased episodic memory outcome has been linked to Val*COMT* alleles (Bertolino et al., 2006; de Frias et al., 2004; Krach et al., 2010). Neuroimaging during memory processing revealed this finding to parallel reduced hippocampal activation and its coupling with PFC during memory retrieval (Bertolino et al., 2006). Hippocampal grey matter volume is reportedly reduced via Val*COMT* allele (Honea et al., 2009), but its implications on prefrontal anatomy have yielded mixed reports (Honea et al., 2009; Tian et al., 2013).

The advantages related to Met*COMT* allele in cognitive functions do not comprise tasks involving affect and emotional processing. Instead, Val*COMT* carriers have shown easier utilization of emotional information in valence evaluation (Swart et al., 2011), more accurate recognition of negative facial expressions (Weiss et al., 2007) and relatively better memory for aversive pictures (Gibbs, Bautista, Mowlem, Naudts, & Duka, 2014; Naudts, Azevedo, David, van Heeringen, & Gibbs, 2012). Additionally, under acute stress, carrying Val*COMT* alleles may prove advantageous in working memory tasks (Buckert, Kudielka, Reuter, & Fiebach, 2012). On the level of neural activity, Met*COMT* allele carriers have shown elevated prefrontal-limbic activation in response to negative stimuli which has been interpreted as less efficient emotional processing (Domschke et al., 2012; Smolka et al., 2005). Convergently, Val*COMT* allele associates with higher PFC activation during executive and mnemonic tasks but lower PCF activation during emotional paradigms (Mier, Kirsch, & Meyer-Lindenberg, 2010). The Val158Met-related discrepancies in executive vs. emotional processing have been related to divergent dynamics between tonic and phasic dopamine levels: higher tonic dopamine along Met*COMT* alleles favor stable task demands (cognition) whereas Val*COMT*-related phasic activity underlies dynamic capabilities (emotion) (Witte & Flöel, 2012).

Studies on sleep and cognition have provided intriguing interactions with *COMT* genotype. In a paradigm of chronic partial sleep deprivation, those homozygous to Met*COMT* allele displayed pronounced homeostatic sleep drive, compared to Val*COMT* carriers (Goel, Banks, Lin, Mignot, & Dinges, 2011). In that study, sleep deprivation did not induce Val158Met-driven differences on tasks of executive function. This is in contrast to a study deploying total sleep deprivation, where sleep-deprived Val*COMT* homozygotes fared relatively worse in a task of adaptive decision making (Satterfield et al., 2018). In the light of these observations, the lack of studies examining how Val158Met interacts with sleep on memory retention becomes obvious. This perspective gains momentum from a report indicating that fast spindle density, an acknowledged biomarker of memory consolidation (Rasch & Born, 2013), is dose-dependently reduced along Val*COMT* alleles (Schilling et al., 2018).

Taken together, two extensively studied gene polymorphisms, *COMT* Val158Met and *BDNF* Val66Met, are shown to moderate sleep, memory and emotional processing. This provokes intriguing speculation whether sleep and the related microstructural events influence memory consolidation equally across individuals, or how inherited factors possibly determine how beneficial sleep is for retention.

# 3 AIMS OF THE STUDY

Accumulated research strongly demonstrates that memory retention is supported by sleep. This is caused by both protection from interference and the consolidation of labile memory traces. The latter is often attributed to oscillatory events during NREM sleep, such as sleep spindles. The synchrony between sleep spindles and slow oscillations have been under keen focus recently, and extending this research to different settings is warranted. Few studies thus far have addressed if individual factors, genes of neural plasticity in particular, interact with sleep's influence on memory outcome. Finally, what is the role of NREM oscillations in the selective off-line consolidation of memories? Hence, the following study aims are covered in this thesis:

- To study the associations between overnight learning and active consolidation mechanisms during NREM sleep (Studies I, III and IV)
- To study how overnight recognition accuracy associates with *BDNF* Val66Met and *COMT* Val158Met and their interaction with sleep spindle-related memory consolidation (Study I and IV)
- To examine how the ratio between wake and sleep interacts with *BDNF* Val66Met and *COMT* 159Met on overnight recognition accuracy (study II)
- To explore how the affective strength and encoding difficulty of the memorized material associate with overnight learning (III and IV)

# 4 MATERIALS AND METHODS

## 4.1 PARTICIPANTS

The participants for Studies I, II and IV were recruited from an urban community-based cohort (Glaku) initially consisting of 1049 infants born between March and November 1998 in Helsinki, Finland (Strandberg, Jarvenpaa, Vanhanen, & McKeigue, 2001). Several publications have been done on the cohort including ones where sleep characteristics have been associated with, for example, cortisol response (Pesonen et al., 2012) and neurocognitive function (Kuula et al., 2015; Pesonen, Ujma, Halonen, Räikkönen, & Kuula, 2019b). The data collection for the studies in this thesis was conducted between November 2014 and December 2015 and aimed to investigate especially sleep and cognition. Receiving a 50 € monetary compensation, 196 adolescents participated in the follow-up. Out of these, 173 were genotyped in the previous follow-up. Technically valid data was obtained from 151 (Study I), 161 (Study II) and 153 (Study IV) participants, depending on whether sleep microstructure was examined in the concerned study.

In Study III, the initial sample consisted of 29 young adults (23 females) living in the capital area of Finland. The participants were recruited through different channels; 11 belonged to the previously studied *SleepHelsinki!* cohort[1], 15 were University of Helsinki students, contacted *via* e-mail lists and social media channels, and three participants were found through personal contacts. All participants received a 100 € monetary compensation for their participation. Measurements were performed between June 2020 and January 2021.

Data from two different samples were used in this thesis for two reasons. First, it was in interest to examine how overnight memory outcome related with the assumed consolidation mechanisms in different age groups (mid/late adolescents and young adults). Second, the level of experimental control between the samples differed. Whereas the collection on Glaku was conducted in natural home circumstances with minimally intercepting daily routines and schedules of the participants, Study III aimed for more precisely controlled experimental setting. To an extent, this enabled to validate methodology and compare results across the studies. The following chapters describe the methodology in detail.

[1] https://clinicaltrials.gov/ct2/show/NCT02964598

## 4.2 STUDY FLOW (I, II AND IV)

The in-home assessment started in the evening (mean 6:16 p.m., SD = 27 min) with questionnaires about factors possibly affecting testing, e.g. native language, handedness and potential handicaps. The participants also filled Pubertal Development Scale (Petersen, Crockett, Richards, & Boxer, 1988). Then a trained research nurse administered a cognitive assessment and the encoding phase of the visual memory task. The mean time of encoding was 7:28 p.m. (SD = 30 min). The polysomnography (PSG) device was then set up, and the subjects were instructed to follow their typical daily routines and sleep schedule. The next morning, the research nurse detached the PSG device and administered the memory retrieval, the mean time being 8:41 a.m. (SD = 1 h 20 min) See Figure 2 for a schematic illustration of the study night.

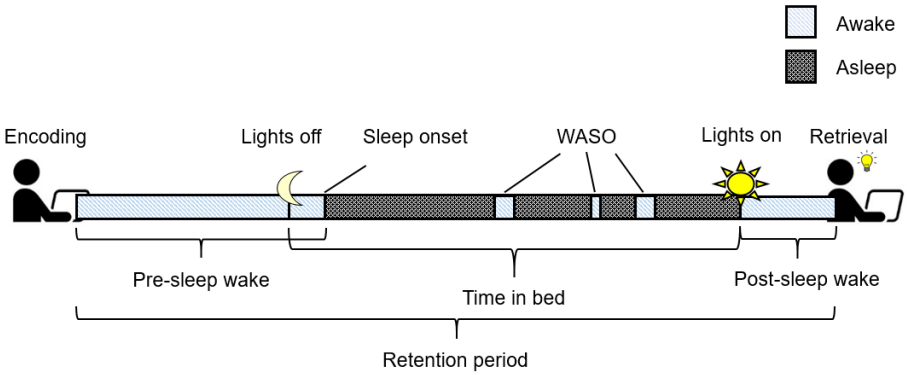


**Figure 2.** The study flow in Studies I, II and IV. WASO = wake after sleep onset. Reproduced with the permission of the copyright holder (Neurobiology of Learning and Memory).

### 4.2.1 PICTURE RECOGNITION TASK

The stimuli in the recognition task consisted of pictures from the International Affective Picture System. The pictures are rated on nine-point scales for emotional arousal (1 = calm, 9 = exciting) and valence (1 = negative, 5 = neutral, 9 = positive) (Lang, Bradley, & Cuthbert, 2005). In this thesis, 200 pictures were divided into 100 target and 100 foil pictures. The target pictures were displayed for 1000 ms on a 14" laptop screen, followed by blank black screen lasting 1500 ms. The following morning, the 100 target pictures, mixed with the 100 unseen foil pictures, were displayed to the participants in a random order. In case of recognition, the participants were instructed to press space bar as quickly as possible. The simple go/no-go paradigm was chosen in order to minimize any confusion during retrieval – the measurements were carried out in a home setting within the community-based adolescent sample.

Only responses given while the picture was visible (1000 ms) were regarded. The research nurse monitored that each participant focused on the task.

The categorization of the pictures was based on either their normative arousal values (Study I) or on both arousal and valence values (Studies II and IV). In Study I the pictures were categorized into two sets (high *d'*, low *d'*) that diverged by their arousal (calm–exciting dimension) ratings: the mean normative arousal of the high and low arousal picture sets were 5.68 (5.00–7.35) and 3.47 (2.28–3.99), respectively (differing significantly in one-way analysis of variance, $p < 0.01$). The mean valence ratings were balanced between the sets (mean valence of high and low arousal pictures were 5.75 and 5.84, respectively; $p = .63$).

In Studies II and IV the pictures were divided into categories by both arousal and valence ratings into two levels of arousal (low / high; LA / HA, respectively) and three levels of valence (negative / moderate / positive; NV / MV / PV, respectively). The mean normative arousal was 3.47 (SD = 0.43) in the LA category and 5.68 (SD = 0.55) in HA category ($p < 0.001$). The mean normative valence values in NV, MV and PV were 4.18 (SD = 0.56), 5.98 (SD = 0.52) and 7.23 (SD = 0.37), respectively ($p < 0.01$). Arousal values were balanced between the valence categories ($p = .63$), and valence values were balanced between the arousal categories ($p = .90$). The mean arousal and valence ratings were balanced between target and foil pictures ($p = .74$ and $p = .68$, respectively).

Recognition accuracy (*d'*) was calculated for all picture categories. The measures of *d'* denoted the difference between the hit rate (standardized proportion of correctly recognized target pictures) and the false alarm rate (standardized proportion of incorrectly recognized foil pictures) (Stanislaw & Todorov, 1999). Loglinear approach was applied due to false alarm rates of 0 (Hautus, 1995). In addition to the recognition accuracy analyses in Studies I, II and IV, supplementary analyses where either hit rate or false alarm rate are included in Chapter 5.6.

## 4.3 STUDY FLOW (III)

The participants completed electronic questionnaires concerning background data [Beck Depression Inventory (BDI) (Beck, Steer, & Brown, 1996), General Anxiety Disorder-7 (GAD-7) (Williams, 2014), learning impairments, health status] after enrolling to the study. On Day 0 (Figure 3), the participants retrieved the actigraphy from the laboratory. All participants slept at home the night between Day 0 and 1, but were allowed to choose whether the study night (between Day 1 and 2) measurements were conducted in the sleep laboratory or at the participant's home. This was done to mitigate

any reluctance for participating in the study during the COVID-19 pandemic. 15 participants chose laboratory measurement. In the evening of Day 1 (~8 pm), the research assistant met the participants, and they underwent the first metaphor encoding. 10 minutes later, immediate cued recall took place. PSG device was then attached, and the participants had an eight-hour sleep opportunity between ~11 pm and ~7 am. The first delayed recall was administered the next morning (~8 pm). Briefly after, the second metaphor encoding and immediate recall were done. The participants spent the Day 2 in their typical activities. The final delayed recall took place at the evening (~8 pm) of Day 2. See Figure 3 for the study process.

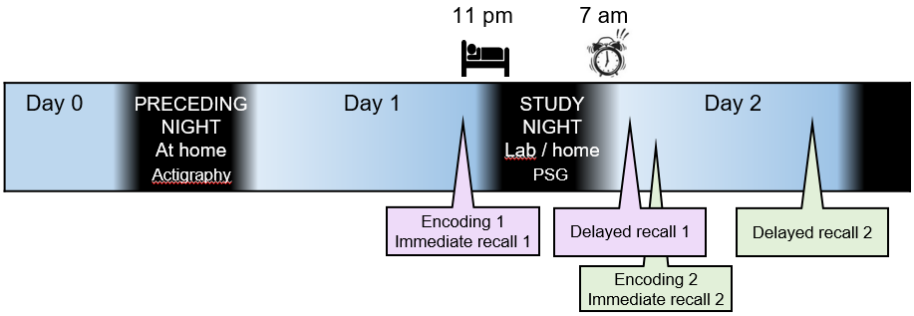


**Figure 3.** The study flow in Study III. PSG = polysomnography. Reproduced with the permission of the copyright holder (Frontiers in Behavioral Neuroscience).

### 4.3.1 CUED METAPHOR RECALL

The retention of novel verbal metaphoric associations has remained largely unstudied regarding sleep and memory, whereas numerous studies have applied more conventional word pair tasks (Denis et al., 2021; Hahn et al., 2020; Payne et al., 2012b; Studte et al., 2017). Imaging studies suggest that the processing of metaphors is implicated with more widespread brain activation, relative to non-metaphors (Bambini, Gentili, Ricciardi, Bertinetto, & Pietrini, 2011). Moreover, novel linguistic associations recruit brain bilaterally in contrast to left-lateralized familiar verbal associations (Arzouan, Goldstein, & Faust, 2007; Bohrn, Altmann, & Jacobs, 2012; Diaz & Eppes, 2018). Thus, metaphoric associations were considered suitable material for examining whether memory retention associated with inter-spindle synchrony, i.e. the synchrony between sleep spindles that emerged simultaneously in different EEG channels (defined in Chapter 4.6.5).

The memory task material in Study III consisted of two sets of 48 metaphors: one for overnight condition and for over day condition. Each set

was divided into 16 and 32 metaphors to immediate and delayed, respectively. The metaphors were selected based on a work on psycholinguistic dimensions (Herkman & Service, 2008), where participants evaluated non-conventional metaphors in nine dimensions (scale 1–7), including easiness (how easy a metaphor was to envision) and liveliness (how vivid and detailed the metaphor was). To eliminate bias in memory performance due to metaphor difficulty, the two sets were balanced in the ease dimension (t-test $p = .93$), the range of normative easiness being 2.38–5.84 and 2.52–5.90 in the two sets. The presentation order of these sets was counterbalanced. The subsets of immediate and delayed recall were also balanced ($p = .96$). For the analyses, the easiness values were inverted to represent metaphor difficulty. For example, the metaphor "(A) malicious remark is a bullet" had lower difficulty (2.98) than the metaphor "(A) clever joke is (a) splint" (5.36). The parentheses denote that there are no articles in Finnish.

During encoding, the participants were displayed 48 written metaphors on a computer screen, and instructed to form a mental image of the metaphors. Each metaphor was displayed for 4.25 s, with a 1.5-s interval until the next metaphor appeared. The participants underwent three encoding rounds.

The delay between encoding and immediate recall was 10 min (16 metaphors), and 12 h regarding the delayed recall (32 metaphors). During the recall, the participants were displayed the beginning of a metaphor on the computer screen [(e.g., "(A) touch is (an)"] in a random order and were asked to type the missing (last) word (e.g., "insect"). Responses were scored such that 1 point was given for the correct word (plural forms and words with simple typographical errors were counted as correct), and 0.5 points were given in case of a synonym (e.g., "bug") or a higher/lower abstraction of the correct word (e.g., "mosquito"). The memory retention outcome was calculated by subtracting the percentage of correct responses in immediate recall from the percentage of correct responses in delayed recall. This resulted in change scores (ΔSleep and ΔWake) corresponding to the delayed condition.

## 4.4 GENOTYPING (STUDY I, II AND IV)

The genotyping of the Glaku cohort was done during the follow-up during 2009-2011. Regarding the sample in Study II, DNA was obtained from blood (4.3 %) and saliva samples (95.7 %). Genotyping was performed with the Illumina OmniExpress Exome 1.2 bead chip at the Tartu University, Estonia, in September 2014 according to the standard protocols. The frequencies of GG (Val/Val), GA (Val/Met) and AA (Met/Met) genotypes were assessed for both Val66Met and Val158Met.

The genotyping of *BDNF* Val66Met showed success rate ≥ 95 %, minor allele frequency of 0.16, and was in Hardy–Weinberg equilibrium (p-value > 0.05). In the samples (Study II / Study I and IV), there were 108/105, 45/41 and 8/8 of GG (Val/Val), GA (Val/Met), AA (Met/Met) genotypes. *COMT* Val158Met showed genotyping success rate ≥ 95 %, minor allele frequency of 0.41, and was in Hardy–Weinberg equilibrium (p-value > 0.05). In the analytic samples, there were 28/27, 76/70 (47 %), and 57/56 of GG (Val/Val), GA (Val/Met), AA (Met/Met) genotypes.

## 4.5 GENERAL COGNITIVE ABILITY

Previous research has shown that 'intelligence' not only correlates with learning (Alexander & Smales, 1997) but also with spindle characteristics (Bódizs et al., 2005; Fogel & Smith, 2011; Hahn et al., 2019; Schabus et al., 2006); but see also (Ujma, 2018), and importantly, the learning-induced changes in spindle activity (Schabus et al., 2006; Schabus et al., 2008). To assess general cognitive abilities (Studies I, II and IV) a shortened version of the Wechsler Adult Intelligence Scale III (Wechsler, 1997) was administered. The assessment included five subtests, administered in the following order: Vocabulary, Block Design, Similarities, Matrix Reasoning and Digit Span. General cognitive score (or full-scale intelligence quotient, FSIQ) was calculated by averaging the Z scores of the subtests.

## 4.6 SLEEP MEASUREMENT

### 4.6.1 POLYSOMNOGRAPHY

PSG was deployed in all studies. The recordings were performed using either SOMNOscreen plus (Studies I, II, III and IV) or SOMNOscreen HD (Study III) (SOMNOmedics GmbH, Randersacker, Germany). The trained research nurse attached gold cup electrodes at the following EEG locations: frontal (F) hemispheres F3 and F4; central (C) C3 and C4; occipital (O) O1 and O2; mastoid (A1, A2). Electro-oculogram and chin electromyogram were measured using disposable adhesive electrodes (Ambu Neuroline 715; Ambu A/S, Ballerup, Denmark), with two locations for EOG and three locations for EMG. An online reference (Cz) and a ground electrode in the forehead were used. The sampling rate was 256 Hz (the hardware filters for SOMNOscreen plus were 0.2–35 Hz). PSG data were scored manually using the DOMINO program (v2.7 or 2.9; SOMNOmedics GmbH, Germany) in 30-s epochs into N1, N2, N3 (SWS), REM, and wake according to AASM guidelines (Iber et al., 2007). Movement arousals were marked.

In all studies, the PSG data on sleep duration (or total sleep time, TST), nightly wake (represented as sleep efficiency or wake after sleep onset, WASO) and sleep stage-specific duration or percentage were defined. In studies I, II and IV this data was compared between genotypic subgroups. In Study II, where the inter-individual variability in sleep/wake measures was the basis of the predictor values, specific measures for sleep percentage (Sleep%, i.e. the proportional time spent asleep during the retention period) and total wake time (TWT, i.e. the time spent awake during the retention period) were calculated. In addition, the time spent awake between encoding and sleep onset (pre-sleep wake) as well as between awakening and retrieval (post-sleep wake) were used in Study II. Figure 2 displays the schematic illustration of how sleep/wake measures were obtained.

For spindle and SO analyses, the manually scored PSG signals were converted to EDF format in DOMINO software and then further analyzed using the functions of EEGlab 14.1.2b (Delorme & Makeig, 2004) running on MATLAB R2018a (MathWorks, Inc., Natick, MA, United States). All signals were digitally band-passed and filtered offline from 0.2 to 35 Hz (with a Hamming windowed sinc zero-phase FIR filter; cutoff, -6 dB), at 0.1 and 35.1 Hz, respectively, and re-referenced to the average signal of A1 and A2 electrodes. Electrodes located at F3, F4, C3, and C4 were included in further analyses.

### 4.6.2 SLEEP SPINDLE DETECTION

Sleep spindles are commonly detected with automated algorithms that process EEG data and spot deviations (i.e. spindles) based on thresholds for frequency, amplitude and duration. Sleep spindles were examined in Study I, III and IV, although with slightly different frequency bands and sleep stage focus. The frequency bands for detecting sleep spindles in Study I and IV were 10–13 Hz (slow spindles) and 13–16 Hz (fast spindles), whereas 12–16 Hz band was used in Study III. In Studies I and III, N2 and N3 spindles were detected separately. Additionally, Studies III and IV investigated NREM spindles in a combined fashion (N2 + N3).

The detection was implemented with MATLAB R2018a (MathWorks, Inc., Natick, MA, United States) and conducted as follows. The pre-processed EEG data were band-pass filtered to the desired frequency band, e.g. 12–16 Hz. From the filtered signal, spindles were extracted with method adapted from an automated detection algorithm described by Ferrarelli and colleagues (Ferrarelli et al., 2007). The method deploys a threshold-based detection, where amplitude elevations of the band-pass filtered signal are required surpass the channel-specific upper threshold and to stay above the lower threshold for a specified time. The upper detection threshold was defined by

multiplying the channel's band-pass filtered signal's mean absolute amplitude by 5. In case of surpassing that threshold, the putative spindle's amplitude was required to stay higher than the mean channel amplitude multiplied by 2 for 250 ms in both directions from the peak maximum, resulting in a minimum spindle duration of 0.5 s. The maximum spindle length was set to 3.0 s and the maximum peak amplitude to 200 μV. To prevent false alarms, the signal amplitude between spindles was required to stay under the lower threshold for 78.1 ms, the approximate duration of one period of sine at 13 Hz. Finally, all spindle-like bursts that occurred during arousals were excluded. Sleep stage-specific spindle densities were calculated by dividing the spindle number by the minutes spent in the concerned sleep stage. For most analyses, the electrode-wise spindle densities were averaged to represent frontal (F3 and F4) or central (C3 and C4) spindle densities.

### 4.6.3 SLOW OSCILLATION DETECTION

In Studies III and IV NREM SOs were detected with an adapted algorithm developed by Ngo and colleagues (Ngo et al., 2015) using the Wonambi EEG analysis toolbox (Piantoni & O'Byrne 2021; Wonambi: EEG analysis toolbox[2]). First, the signal low-pass filtered at 3.5 Hz. All negative and positive amplitude peaks were identified between two subsequent positive-to-negative zero-crossings, comprising a full phase cycle. Zero-crossing intervals within the duration of 0.8–5 s were included (0.2–1.25 Hz frequency range). Finally, mean values for positive and negative peak potentials were calculated, and these events were denoted as SOs if 1) the negative peak was lower than the mean negative peak and 2) the positive-to-negative peak amplitude difference exceeded the mean amplitude difference.

### 4.6.4 SLOW OSCILLATION-SPINDLE COUPLING

The synchrony between slow oscillation and sleep spindles was investigated in Studies III and IV. The synchrony was operationalized as phase-amplitude coupling (PAC; Study III) or event-based detection of spindle amplitude peaks within a SO cycle (Study III and IV).

PAC is cross-frequency coupling approach that examines electrical brain activity for statistical dependence between the phase of a low-frequency component (e.g. slow oscillations) and the power of the high-frequency oscillation (e.g. sleep spindles) (Canolty & Knight, 2010). The PAC measure used in this thesis was modulation index (MI), estimated with an adaptation of the Kullback–Leibler distance proposed by Tort and colleagues (Tort,

[2] https://github.com/wonambi-python/wonambi

Komorowski, Eichenbaum, & Kopell, 2010). Methods from Tensorpac (Combrisson et al., 2020) were used for the purpose in Study III. Channel-wise MIs from all N2 and N3 sleep epochs were calculated, using SO range (0.2–1.25 Hz) as the phase frequency and spindle range (12–16 Hz) as the amplitude frequency range. The phase was first divided into 18 bins, each 20°. Then, the mean spindle range amplitude was computed for all bins. The empirical probability distribution was calculated by dividing the measured amplitude inside each bin by the sum of the bins. MI represents the difference between this distribution and the uniform distribution. To noise-correct the PAC measure, a surrogate distribution was obtained by splitting the amplitude blocks at a random time point, swapping them, and calculating a PAC measure with the original phase data (Bahramisharif et al., 2013). The distribution of surrogate values was created by repeating this procedure 1,000 times. Finally, subtracting the surrogate means from the uncorrected MIs and then dividing by the surrogate standard deviation resulted in corrected PAC values.

In Study III, PAC was calculated to represent the degree of how the high-frequency amplitude is modulated by the low-frequency phase in a non-event-specific manner. Directional, event-based SO-spindle coupling was done as follows (Studies III and IV): First, all spindles whose amplitude peaked between the zero-crossings of a SO cycle were identified (i.e., SO-spindles). Next, the EEG signal was band-pass filtered to 0.2–1.25 Hz and Hilbert-transformed, and the instantaneous phase at the SO-spindle amplitude peaks were extracted.

In Study III, the examined variables were SO–spindle% (i.e., the percentage of spindles occurring during SO, out of all spindles), the circular mean angle in degrees (i.e. mean preferred phase, $PP_{Mean}$), and the percentage of spindle peaks (out of all SO–spindle peaks) occurring proximal to the positive SO peak (±45° from 0°), i.e. Upstate%. In Study IV, SO-spindle coupling tendency and phase were examined with SO-spindle%, mean SO phase of SO-spindle peaks and resultant vector length (RVL). The associations between coupling and memory outcome in Study IV were studied specifically with *directional* coupling measures, both relative and absolute. As a relative measure was the mean coupling distance that was defined by averaging the absolute phase differences in radians, obtained with CircStat toolbox (Berens, 2009), between individual spindle peaks and either 0° (fast spindles) or 90° (slow spindles). While coupling distance is a relative measure and does not capture the amount of the concerned events, the number of SO-spindles peaking at different phases within a SO cycle was also calculated. To this end, the SO cycle was divided into eight bins of equal phase angle, i.e. 45° each, starting from the negative peak at -180° into Bin1 (-180° to -135°), Bin2 (-135° to -90°), Bin3 (-90° to -45°), Bin4 (-45° to 0°), Bin5 (0° to 45°), Bin6 (45° to 90°), Bin7 (90° to 135°) and Bin 8 (135° to 180°). After that, the number of sleep spindle peaks occurring within each bin was counted (Figure 4). The

analyses regarding memory outcome focused *a priori* on fast SO-spindles peaking within ±45° from 0° (i.e. Upstate#) or slow SO-spindles peaking within ±45° from 90° (i.e. Descending#).

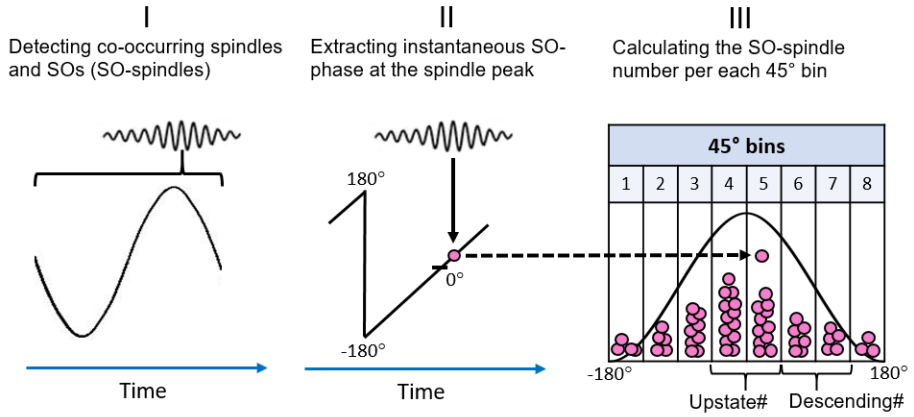


**Figure 4.** The delineation of slow oscillation-spindle binning (Study IV). Reproduced with the permission of the copyright holder (Behavioural Brain Research).

### 4.6.5 INTER-SPINDLE SYNCHRONY

Study III examined inter-spindle synchrony. To define inter-spindle synchrony in separate channels, simultaneous spindles between the F3, F4, C3, and C4 channels were detected. This was done in the following steps. (1) Proceeding the EEG data chronologically, when a spindle emerged after a spindle-free period in any channel, it was examined if another spindle in any other channel overlapped the first one (that is., peaked within the duration of the first spindle). (2) In the case of overlap, it was examined which spindle peaked first and nominated it as *the seed* spindle. (3) Any spindle that overlapped the seed spindle was nominated as a *trailing* spindle. Thus, a seed spindle could occur alone or be temporally overlapped by one, two, or three (different channels) trailing spindles. The overlap direction (i.e., seed to trailing; e.g., F3–C3) was recorded. For each electrode pair (seed–trailing), the following values were defined: propagation latency, overlap duration, and propagation density (PD), which represents the probability of a certain pair (e.g., F3–C3) to occur among all seed spindle events in the channel (e.g., F3) (Figure 5). To include only those seed–trailing pairs where the overlap delay could plausibly be underlain by wave propagation, all pairs in which the delay between the peaks was below 8 ms were excluded. The lower limit was based on a previous study on spindle propagation (O'Reilly & Nielsen, 2014).

Phase lag index (PLI) (Stam, Nolte, & Daffertshofer, 2007) was computed for all seed–trailing pairs that overlapped by more than 0.3 s (Figure 5). For the pairs of overlapping band-pass-filtered EEG signals, the phase angle in radians for each sample after the Hilbert transform was extracted. The asymmetry of phase differences over the signal pairs was obtained with the signum function, resulting in pair-specific raw PLIs ranging from 0 (random phase difference) to 1 (fixed phase difference). Again, this concerned spindle pairs that did not overlap instantly (< 8 ms). The obtained raw PLIs were further contrasted with randomized spindle-PLIs to highlight the synchrony between overlapping spindles, in contrast to non-overlapping spindles. To this end, the contrast spindle-PLIs were created by calculating the PLI values between each seed spindle and a randomly chosen spindle event from the same participant; this procedure was repeated 100 times. Channel-pair-wise corrected PLIs (cPLIs) were obtained by subtracting the contrast PLIs from the raw PLIs. The cPLIs were categorized according to the direction (e.g., F3–C3) for each participant.

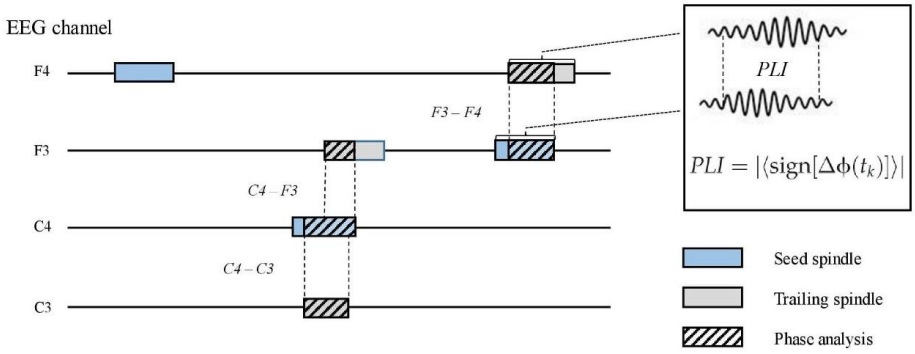


**Figure 5.** Parametrizing inter-spindle synchrony (Study III). Seed spindles (light blue) may be overlapped by one or more spindles in other electroencephalography channels (trailing spindles, light gray). Phase lag index (PLI) between the seed and trailing spindles was calculated. Reproduced with the permission of the copyright holder (Frontiers in Behavioral Neuroscience).

For memory outcome analyses, both PD and cPLI values were averaged into frontal to central (F–C), central to frontal (C–F), left to right (L–R), and right to left (R–L) means. The averaging concerned only non-diagonal electrode pairs (for example, F-to-C, including F3–C3 and F4–C4, and not F3–C4 or F4–C3).

### 4.6.6 ACTIGRAPHY

Actigraphy consists of measuring various aspects of movement with e.g. a wrist-worn device. The device's functionality is based on accelometer, whose recorded data gives base to estimate different levels of activity, including sleep. Actigraphy data was used in the Studies II and III. In the Study II, Participants were instructed to wear Actiwatch AW7 (CamNtech Ltd, Cambridge, United Kingdom) for 10 consecutive days. Bedtime values containing at least 5 valid measurement nights (N = 154) were averaged to represent the habitual bedtime. In the Study III the participants wore Philips Actiwatch 2 actigraphies for 2 days in order to screen for highly deviant sleep durations before the actual test night.

## 4.7 COVARIATES

Sex was controlled for in all studies. This was based on earlier research displaying sex differences in neurocognitive function and sleep spindle activity (Pesonen et al., 2019b).

In study I where the associations between memory outcome and sleep EEG characteristics were investigated, both sleep duration and the time spent awake during the retention period were controlled for. This was done in order to avoid the highly variable sleep/wake measures from confounding with the studied associations. Additionally, general cognitive ability was used as a covariate in Study I. These covariates were included in the Model 2, whereas only sex was controlled for in the Model 1.

In Study II where the durations of sleep (TST, N3 and REM) and wake (total, pre- and post-sleep wake) were used as independent variables, their effects were reciprocally controlled to avoid their common variance from confounding the studied associations. Moreover, additional analyses were run while controlling for 1) the length of retention period, 2) the habitual bedtime of the participants, 3) sleep duration in the night preceding the study and 4) general cognitive ability.

In Study III, a 'control' model was created in order to control for sleep duration, BDI and GAD-7 scores. Moreover, supplementary tests were run deploying spindle density as a covariate.

In Study IV, the covariates included sex, sleep duration and the total time spent awake. Supplementary tests were run with controlling for general cognitive ability, spindle density, SO amount or SO-spindle%.

## 4.8 STATISTICAL ANALYSES

In Studies I, II and IV, genotypic differences in sleep characteristics, sleep spindle and SO values, SO-spindle coupling measures, age, pubertal development and FSIQ were tested with one-way analysis of variance (ANOVA). Sex ratio between genotypic subgroups was tested with Chi-squared test.

In Study I, mixed ANOVAs were used in assessing whether the between-subject variable genotypic subgroup (two levels, $Val_{BDNF}$ homozygotes, $Met_{BDNF}$ carriers) affected recognition accuracy (two-level within-subject, high *d'* and low *d'*). Linear regression analysis was used to test the significance of sleep spindles (independent) on high *d'* and low *d'* (dependent) for the whole sample and separately for the allelic groups. To test if the associations between each spindle variable and recognition task scores differed between the genotypes, two-way ANOVA was used to compare the regression slopes with an interaction term of 'spindle density variable x genotype'.

In Study II, a mixed ANOVA was applied to test how recognition accuracy *d'* (dependent variable) was affected by picture category (within-subject variables; 2 levels of arousal, 3 levels of valence). Second, the effect of sleep/wake variables (continuous independent variables) on recognition accuracy in the whole sample was examined, as well as their interaction with picture category. To this end, four separate models for 1) Sleep%; 2) TWT and TST; 3) N3 and REM; 4) Pre- and post sleep wake were run. Third, genotypic main effects and 'genotype x picture category' interaction were then tested (without sleep/wake variables) including either *BDNF* Val66Met or *COMT* Val158Met as between-subjects variable (two levels for both *BDNF* and *COMT*, i.e. $Val_{BDNF}$ homozygotes and $Met_{BDNF}$ carriers; and $Met_{COMT}$ homozygotes and $Val_{COMT}$ carriers, respectively). Finally, the interaction between genotype and Sleep%, TWT and TST were tested one-by-one, including the interaction term along with the main effects in to the model. Follow-up analyses were either within-subject ANOVAs (for picture category effects on *d'*) or regression analyses with the averaged *d'* (across picture categories) as the dependent variable.

In Study III, the analyses evaluating metaphor difficulty level considered one metaphor an observation unit. The association between recall probability in immediate recall and metaphor difficulty was tested using one-way ANOVA. For delayed recall, a mixed ANOVA model was constructed, with recall probability (for both sleep/wake conditions) as dependent variables and metaphor difficulty as a continuous independent variable in order to examine the main effects of metaphor difficulty as well as its interactions with delay conditions. Repeated measures ANOVA was used to test if immediate recall scores differed between evening and morning recalls, and if the delay

condition affected the delayed retention outcome (ΔSleep and ΔWake). The associations between memory retention (ΔSleep and ΔWake), SO-spindle coupling variables (MI, SO-spindle%, and Upstate%), and inter-spindle variables (PD, cPLI) were tested using linear regression analyses. A quadratic regression was used to examine the association between memory retention and $PP_{Mean}$ because this variable represents values (degrees) distributed on a circular (not linear) plane. Rayleigh's test of non-uniformity was used to test the circular distribution of $PP_{Mean}$ values at the group level. Frontal and central NREM $PP_{Mean}$ distributions was compared using the Watson-Williams test. The SO-spindle coupling variables in N3 and N2 sleep were compared using a pairwise t-test. The association between PD and cPLI grand mean was tested using Pearson's correlation. Statistical differences between the variable means was examined using Friedman's test, and this test was conducted separately for PD and cPLI.

In Study IV, paired-samples t-tests were used to compare RVL and coupling distance between 1) fast and slow spindles and 2) between frontal and central fast spindles. Rayleigh's test of non-uniformity was used to test the circular distribution of the mean SO-spindle phase values. We compared mean phase distributions between 1) fast and slow SO-spindles, 2) genotypic subgroups and 3) frontal and central SO-spindles with Watson-Williams test. Mixed ANOVAs were used to test the associations between recognition accuracy (2 levels of arousal, 3 levels of valence) and SO-spindle measures (coupling distance and Upstate#/Descending# as continuous independent variables). Genotype (Val66Met or Val158Met) was used as a between-subjects variable when examining the interactions between SO-spindle measures and genotype. Mixed ANOVAs were used to investigate the interactions between SO-spindle measures and the emotional dimensions (arousal and valence) of the picture categories. Follow-up tests exploring the interactions within-group were mixed ANOVAs and linear regressions. In follow-up analyses where several parallel variables were tested, we used false discovery rate (FDR) correction (Benjamini & Hochberg, 1995) with q-value 0.05: 8 tests for mixed ANOVAs between bin-wise SO-spindle amount and overall recognition accuracy, and 48 tests when the associations between SO-spindle bins (8) and picture categories (6) were tested with linear regression. Significant one-way ANOVAs on three subgroups of Val158Met were followed-up with Bonferroni-corrected post-hoc comparisons.

Statistical analyses on linear variables were performed using IBM SPSS Statistics for Windows, version 27.0 (IBM Corp, Armonk, NY, US). CircStat toolbox (Berens, 2009) was used to calculate circular variables (mean phase, RVL, circular distance) and run tests on circular (Rayleigh's test and Watson-Williams test) in Studies III and IV.

## 4.9 ETHICS

The Ethics Committee of the Children's Hospital in Helsinki University Central Hospital approved the Studies I, II and IV. Study III was approved by the Helsinki University Hospital Ethics Committee. In all studies, informed written consent was obtained from the participants. All studies were conducted in accordance with the Declaration of Helsinki.

# 5 RESULTS

## 5.1 SAMPLE CHARACTERISTICS, STUDIES I, II AND IV

Table 1 presents the age, wake and sleep measures and the general cognitive ability of the sample (Study II; N = 161, 90 female subjects / 56 %). No significant differences were found between either *BDNF* or *COMT* subgroups (p-values ≥ 0.130). Sex ratio did not differ between *BDNF* ($p_{\chi^2}$ = .423) nor *COMT* ($p_{\chi^2}$ = .478) subgroups.

**Table 1.** Sample characteristics, compared between the genotypic subgroups (Study II).

| | ALL N = 161 | | | *BDNF* (VH/MC) N = 108/53 | *COMT* (MH/VC) N = 57/104 |
|---|---|---|---|---|---|
| | Mean | SD | Range | p | p |
| Age | 16.89 | 0.12 | 16.64–17.26 | .50 | .30 |
| PDS | 3.25 | 0.39 | 2.20–3.80 | .75 | .99 |
| Sleep percentage % | 57.81 | 8.26 | 23.63–76.57 | .66 | .99 |
| TWT (hh:mm) | 5:36 | 1:20 | 2:18–10:23 | .94 | .90 |
| Before sleep onset | 4:20 | 1:15 | 1:23–9:00 | .97 | .56 |
| WASO | 0:16 | 0:20 | 0:01–3:20 | .39 | .86 |
| After awakening | 1:01 | 0:36 | 0:20–3:23 | .68 | .12 |
| TST (hh:mm) | 7:37 | 1:08 | 3:09–10:45 | .31 | .96 |
| N1 | 0.50 | 0:22 | 0:13–2:05 | .55 | .86 |
| N2 | 3:08 | 0:41 | 1:00–5:24 | .56 | .75 |
| N3 | 2:03 | 0:28 | 0:53–3:20 | .66 | .23 |
| REM | 1:36 | 0:30 | 0:16–2:50 | .19 | .28 |
| Sleep efficiency % | 92.72 | 6.82 | 58.55–98.86 | .49 | .70 |
| Retention length (hh:mm) | 13.23 | 1.12 | 9:50–17:23 | .30 | .85 |
| FSIQ (raw score mean) | 31.02 | 4.25 | 15.40–40.20 | .27 | .09 |

VH = Val homozygote. MC = Met carrier. MH = Met homozygote. VC = Val carrier. SD = standard deviation. p = p-value of the genotypic difference. PDS = Pediatric Development Scale (obtained from Study I). TWT = Total wake time. WASO = wake after sleep onset. TST = Total sleep time. N1–3: Non-rapid eye movement sleep stages 1–3. REM = rapid eye movement sleep. Retention length = The time between picture encoding and retrieval. FSIQ = Full-scale intelligence quotient. Reproduced with the permission of the copyright holder (Neurobiology of Learning and Memory).

Table 2 presents frontal sleep spindle and slow oscillation characteristics in NREM sleep (Study IV; N = 153, 86 female subjects / 56 %). No significant differences were found between either *BDNF* or *COMT* subgroups (p-values ≥ 0.120).

**Table 2.** Frontal sleep spindle and slow oscillation characteristics, compared between the genotypic subgroups (Study IV).

| | ALL N = 153 | | | BDNF (VV/VM+MM) N = 105/48 | COMT (VV/VM/MM) N = 27/70/56 |
|---|---|---|---|---|---|
| | Mean | SD | Range | p | p |
| Fast spindle density | 2.9 | 0.9 | 1.1–5.9 | .91 | .33 |
| Slow spindle density | 4.1 | 0.9 | 0.6–6.8 | .88 | .86 |
| SOs / channel (mean) | 939 | 224 | 474–1513 | .55 | .12 |
| Fast SO-spindle% | 17.6 | 6.0 | 5.8–42.0 | .40 | .89 |
| Slow SO-spindle% | 14.3 | 4.7 | 3.8–30.1 | .16 | .64 |

VV = Val/Val. VM = Val/Met. MM = Met/Met. SD = standard deviation. . p = p-value of the genotypic difference in one-way ANOVA. SO = slow oscillation. SO-spindle% = the percentage of SO-coupled spindles of all spindles. Reproduced with the permission of the copyright holder (Behavioural Brain Research).

## 5.2 SAMPLE CHARACTERISTICS, STUDY III

Table 3 presents sample characteristics, including age, sleep measures, questionnaire scores, and raw memory task scores. We also compared these characteristics between home-measured and laboratory-measured participants, demonstrating higher sleep duration and N3 percentages for those who slept at home ($p$ = .027 and $p$ = .012, respectively).

**Table 3.** Sample characteristics in Study III.

| | Range | Mean | SD | p |
|---|---|---|---|---|
| Age | 19–41 | 22.0 | 4.3 | .173 |
| Sleep duration, previous night (h:mm) | 5:50–8:37 | 7:10 | 0:46 | .021 |
| Sleep duration, study night (h:mm) | 4:18–7:49 | 6:38 | 0:50 | .027 |
| N1 % | 1.4–17.26 | 5.9 | 3.6 | .114 |
| N2 % | 21.6–49.3 | 35.5 | 8.1 | .555 |
| N3 % | 8.2–41.4 | 24.6 | 7.4 | .012 |
| REM % | 7.9–27.9 | 18.2 | 5.1 | .274 |
| WASO (h:mm) | 0:05–2:07 | 0:29 | 0:32 | .980 |
| BDI score | 0–31 | 10.9 | 9.3 | .840 |
| GAD-7 score | 1–15 | 5.4 | 4.0 | .319 |
| Immediate recall, evening | 9.5–16 | 13.2 | 2.0 | .444 |
| Immediate recall, morning | 10–16 | 13.8 | 1.7 | .918 |
| Delayed recall, sleep | 10–31.5 | 25.0 | 6.0 | .537 |
| Delayed recall, wake | 2.5–26 | 17.2 | 5.8 | .475 |

SD = standard deviation. p = p-value of the difference between measurement place (home / laboratory). N1–3: Non-rapid eye movement sleep stages 1–3. REM: rapid eye movement sleep. WASO = wake after sleep onset. BDI = Beck Depression Inventory. GAD-7 = Generalized Anxiety Disorder 7 questionnaire. Reproduced with the permission of the copyright holder (Frontiers in Behavioral Neuroscience).

## 5.3 STUDY I: SLEEP SPINDLES, *BDNF* VAL66MET AND OVERNIGHT VISUAL RECOGNITION ACCURACY

Study I investigated within the Glaku cohort how sleep spindle density associated with overnight picture recognition and whether *BDNF* Val66Met moderated the association. No difference was found in recognition accuracy between $Val_{BDNF}$ homozygotes and $Met_{BDNF}$ carriers (Model 1: $F_{1, 148} = 1.820$, $p = .179$, $\eta_p^2 = 0.012$; Model 2: $F_{1, 145} = 0.903$, $p = .344$, $\eta_p^2 = 0.006$).

In all subjects, recognition accuracy for high arousal (high *d'*) pictures was associated with N2 frontal slow spindles when controlling for sex only (Model 1: B = 0.092, t = 2.205, p = .029. Also, high *d'* associated significantly with frontal fast spindles in both models in the entire sample (Model 1: B = 0.079, t = 2.258, p = .025; Model 2: B = 0.091, t = 2.386, p = .018). In addition, recognition accuracy for low arousal pictures (low *d'*) related significantly with frontal slow spindles (Model 1: B = 0.124, t = 2.626, p = .010); Model 2: B = 0.097, t = 2.106, p = .037). Table 4 shows the associations in Model 2.

Separate examination of the allelic group revealed significant associations in the Val homozygote group. Recognition accuracy in high arousal pictures associated with frontal slow spindle density (Model 1: B = 0.114, t = 2.569, p = .012; Model 2: B = 0.098, t = 2.193, p = .031) and frontal fast spindle density (Model 1: B = 0.122, t = 2.977, p = .004; Model 2: B = 0.124, t = 3.080, p = .003). Regarding low arousal pictures, positive relationships were found between low *d'* and frontal slow spindle density (Model 1: B = 0.147, t = 2.695, p = .008; Model 2: B = 0.114, t = 2.160, p = .033) and frontal fast spindle density (Model 2: B = 0.104, t = 2.155, p = .034). Moreover, the interaction between N2 frontal fast spindles and genotype was significant regarding high *d'* [Model 1: $F_{(1, 146)} = 3.891$, $p = .050$, $\eta p^2 = 0.026$; Model 2: $F_{(1, 143)} = 4.662$, $p = .033$, $\eta p^2 = 0.032$], indicating divergent associations between the genotypes. Table 4 shows the results in Model 2.

**Table 4.** Regression and interaction analyses between overnight recognition accuracy and N2 spindle densities. Results shown for Model 2.

| Spindle density | All | $Val_{BDNF}$ homozygotes | $Met_{BDNF}$ carriers | Val66Met x spindle |
|---|---|---|---|---|
| High *d'* | B (SE) | B (SE) | B (SE) | F |
| Central slow | 0.01 (.06) | 0.05 (.07) | -0.04 (.11) | 0.33 |
| Frontal slow | 0.08 (.04) | 0.10* (.05) | 0.03 (.10) | 1.03 |
| Central fast | 0.07 (.04) | 0.06 (.05) | 0.11 (.10) | 0.31 |
| Frontal fast | 0.09* (.04) | 0.12** (.04) | 0.02 (.09) | 4.66* |
| Low *d'* | | | | |
| Central slow | 0.05 (.07) | 0.06 (.08) | 0.00 (.11) | 0.23 |
| Frontal slow | 0.10* (.05) | 0.11* (.05) | 0.03 (.10) | 1.02 |
| Central fast | 0.05 (.05) | 0.05 (.05) | 0.07 (.10) | 0.00 |
| Frontal fast | 0.06 (.04) | 0.10* (.05) | -0.05 (.09) | 3.23 |

B = Regression analysis coefficient B for spindle density variables in the entire sample (All) and separately for $Val_{BDNF}$ homozygotes and $Met_{BDNF}$ carriers. SE = Standard Error. F = F-value of the interaction term 'Val66Met x spindle'. High *d'* = recognition accuracy as *d'* for high arousal pictures. Low *d'* = recognition accuracy as *d'* for low arousal pictures. Covariates: sex, full-scale IQ, total time awake and sleep duration. ** p < .01. * p < .05. Reproduced with the permission of the copyright holder (Behavioural Brain Research).

Scatterplots in Figure 6 illustrate the associations between frontal fast spindle density and high *d'* separately for $Val_{BDNF}$ homozygotes and $Met_{BDNF}$ carriers. In $Val_{BDNF}$ homozygotes, frontal fast spindle density explains 8.9 % of the variability of high d' scores and 0.1 % in Met carriers.

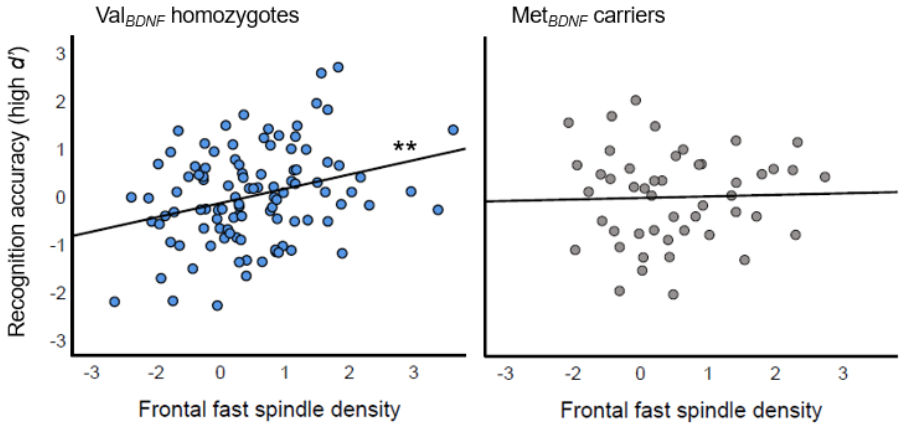


**Figure 6.** Scatterplots (in standardized residuals) showing the associations between fast spindle density and recognition accuracy for high arousal pictures. In the Val homozygote group, the association was significant (p = .004). ** p < 0.01. Reproduced with the permission of the copyright holder (Behavioural Brain Research).

Sleep spindle densities during N3 sleep were not associated with recognition accuracy regarding high or low arousal picture scores in the whole sample nor did they interact with *BDNF* Val66Met (p-values ≥ .124). Regression analyses separately for $Val_{BDNF}$ homozygotes or $Met_{BDNF}$ carriers showed no significant associations (p-values ≥ .077).

## 5.4 STUDY II: SLEEP-WAKE-RATIO, *BDNF* VAL66MET, *COMT* VAL158MET AND OVERNIGHT VISUAL RECOGNITION ACCURACY

First, it was examined if arousal or valence associated with the recognition accuracy of pictures. Both arousal (high/low) and valence (positive/neutral/negative) associated with recognition accuracy ($F = 11.176$, $p = .001$ and $F = 15.366$, $p < .001$, respectively). Higher recognition accuracy was found for high arousal, relative to low arousal, pictures (Bonferroni-corrected $p = .001$). Pictures of positive and negative valence were recognized more accurately than those with neutral valence (Bonferroni-corrected $p = .002$ and $p < .001$, respectively). Figure 7 shows the estimated marginal means of recognition accuracy in each category.

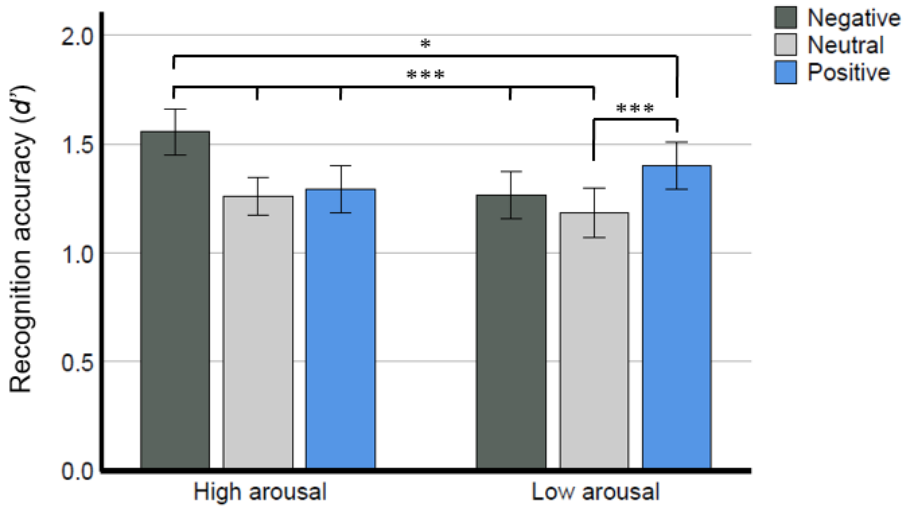


**Figure 7.** Recognition accuracy (*d'*) (estimated marginal means) in different picture categories. Highly arousing, negatively-valenced pictures had higher recognition accuracy than the pictures from any other category. Low-arousing positive pictures were better recognized than low-arousing moderate pictures. *** $p < .001$; * $p < .05$. Reproduced with the permission of the copyright holder (Neurobiology of Learning and Memory).

In the whole sample, Sleep%, TWT and TST on were not associated with recognition accuracy (p-values ≥ .069). The durations of sleep stages (N3, REM) or pre- and post-sleep wakefulness did not associate with recognition accuracy (p-values ≥ .265).

Next, genotypic interaction on the association between sleep/wake variables and recognition accuracy was examined. *BDNF* Val66Met interacted

with Sleep% (F = 8.754, p = .004) and TWT (F = 4.093, p = .045) on picture recognition accuracy. TST did not interact significantly with Val66Met (F = 0.308, p = .580). No significant interactions were observed regarding *COMT* Val158Met (p-values ≥ .136). The interactions are displayed in Table 5.

**Table 5.** The impact of Sleep%, TWT and TST on recognition accuracy in the whole sample, and their interaction with *BDNF* Val66Met and *COMT* Val158Met.

| | All | | *BDNF* | | *COMT* | |
|---|---|---|---|---|---|---|
| | F | p | F | p | F | p |
| Sleep% | 3.447 | .069 | 8.754** | .004 | 0.299 | .586 |
| TWT | 2.092 | .150 | 4.093* | .045 | 0.015 | .904 |
| TST | 0.194 | .661 | 0.308 | .580 | 2.241 | .136 |

*BDNF*/*COMT* = The interaction between *BDNF*/*COMT* genotype and sleep/wake variables on recognition accuracy (*d'*). Sleep% = The percentage of sleep during retention period. TWT = The total time spent awake during the retention period. TST = The total time spent asleep during the retention period. ** p < .01 * p < .05. Reproduced with the permission of the copyright holder (Neurobiology of Learning and Memory).

Follow-up tests separately on $Val_{BDNF}$ homozygotes and $Met_{BDNF}$ carriers showed that the fractioned coefficient of determination ($R^2$) for Sleep% on recognition accuracy was 9.5 % in $Val_{BDNF}$ homozygotes (significant positive association; $R^2$ = 0.095, B = 2.204, t = 3.303, p = .001; $Met_{BDNF}$ carriers: $R^2$ = 0.019, B = -0.735, t = -0.881, p = .383). TWT explained 5.4 % on recognition accuracy in $Val_{BDNF}$ homozygotes ($Val_{BDNF}$ homozygotes: $R^2$ = 0.054, B = -0.104, t = -2.428, p = .017; $Met_{BDNF}$ carriers: $R^2$ = 0.011, B = 0.049, t = 0.741, p = .462). Scatterplots in Figure 8 illustrate the associations between sleep/wake measures and recognition accuracy. A division to pre- and post-sleep wake revealed that wakefulness before sleep onset associated significantly with recognition accuracy (B = -0.101, t = -2.090, p = .039) in $Val_{BDNF}$ homozygotes, whereas wakefulness after awakening did not (B = -0.102, t = -1.252, p = .214).

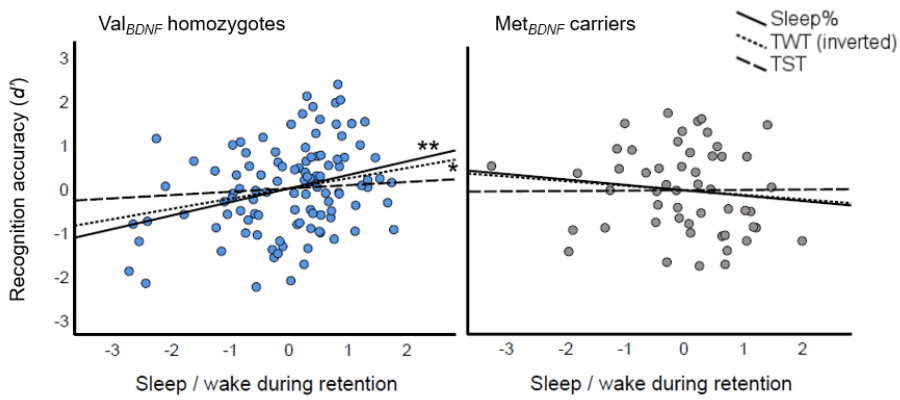


**Figure 8.** The associations between sleep/wake and recognition accuracy. In Val$_{BDNF}$ homozygotes, Sleep% (continuous line, adhering to the markers) and TWT (dotted line, inverted) explained 9.5 % (p = .001) and 5.4 % (p = .017), respectively, of the variation of recognition accuracy. In Met$_{BDNF}$ carriers, none of the sleep/wake regression slopes was significant. TST = total sleep time (dashed line). ** p < .01; * p < .05. Reproduced with the permission of the copyright holder (Neurobiology of Learning and Memory).

The levels of arousal or valence, or 'arousal x valence', did not interact with sleep/wake measures on recognition accuracy (p-values ≥ .335). Likewise, arousal, valence or 'arousal x valence' did not interact with *BDNF* Val66Met (p-values ≥ .076). However, a significant interaction was found between *COMT* Val158Met and arousal (F = 6.706, p = .011) but not valence or 'arousal x valence' (p-values ≥ .094). The follow-up tests for Met$_{COMT}$ homozygotes and Val$_{COMT}$ carriers showed higher recognition accuracy for high, relative to low, arousal pictures in Met$_{COMT}$ homozygotes (F = 13.582, p < .001), whereas arousal level did not associate with recognition accuracy in Val$_{COMT}$ carriers (F = 1.852, p = .177) (Figure 9).

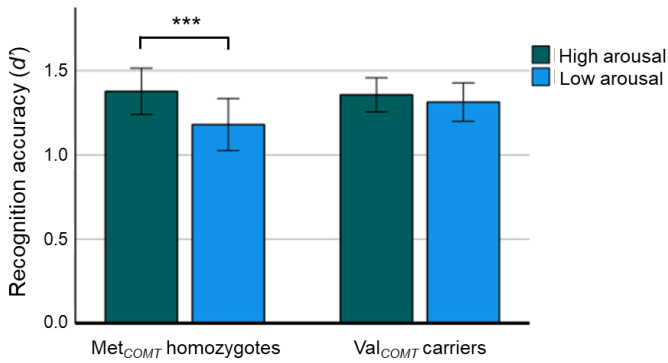


**Figure 9.** In Met$_{COMT}$ homozygotes, recognition accuracy (*d'*, estimated marginal means) was higher for high than low arousal pictures. *** p < .001. Reproduced with the permission of the copyright holder (Neurobiology of Learning and Memory).

## 5.5 STUDY III: OVERNIGHT METAPHOR RETENTION AND SLOW OSCILLATION-SPINDLE COUPLING

The metaphor difficulty level was associated with recall probability in delayed recall ($F = 5.403$, $p = .023$) but not in immediate recall ($F = 1.613$, $p = .214$). The delay condition (sleep/wake) did not interact with difficulty level in terms of recall probability ($F = 0.046$, $p = .831$); that is, the association between difficulty and recall probability did not differ between the conditions. Recall probability as a function of metaphor difficulty level is plotted in Figure 10 A. Retention was significantly better over sleep condition relative to wake ($F = 39.743$, $p < 0.001$; Figure 10 B).

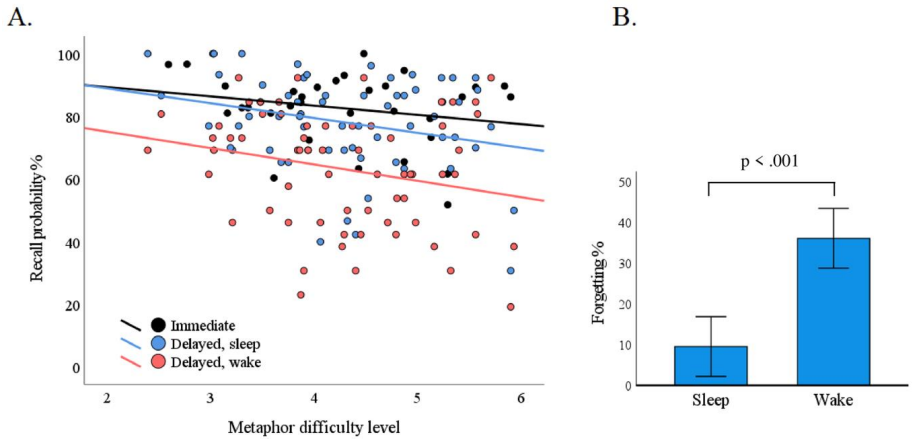


**Figure 10.** The impact of metaphor difficulty and delay conditions on recall performance. (A) Each dot represents a metaphor. The probability for correct responses associated with the metaphor difficulty level in the delayed condition ($p = .023$; blue line, sleep; red line, wake). (B) Less forgetting occurred over sleep condition, relative to wake ($p < 0.001$). Reproduced with the permission of the copyright holder (Frontiers in Behavioral Neuroscience).

Next, SO-spindle coupling was investigated. SO-spindle mean phases ($PP_{Mean}$) were non-uniformly distributed in frontal ($p < 0.001$) and central ($p < 0.001$) derivations. Figure 11 A displays the tendency of mean preferred phase angles to cluster near the SO upstate (0°) in NREM sleep. Frontal and central $PP_{Mean}$ values did not differ (p-values ≥ 0.083). Comparison between N2 and N3 sleep showed that the coupling measures were significantly higher in N3 sleep both frontally and centrally (p-values ≤ 0.010) (Table 6).

**Table 6.** Oscillation characteristics.

| | NREM | | N2 | | N3 | | N2 vs. N3 |
|---|---|---|---|---|---|---|---|
| | Mean | SD | Mean | SD | Mean | SD | p |
| Spindle density F | 4.44 | 0.81 | 4.61 | 0.74 | 4.48 | 0.97 | .347 |
| Spindle density C | 4.59 | 0.76 | 4.72 | 0.79 | 4.62 | 0.87 | .504 |
| SO F | 1,946 | 433 | 728 | 159 | 1,023 | 321 | <.001*** |
| SO C | 1,859 | 390 | 730 | 175 | 978 | 290 | <.001*** |
| SO-spindle% F | 13.7 | 4.4 | 12.7 | 4.4 | 16.0 | 5.3 | <.001*** |
| SO-spindle% C | 12.8 | 4.0 | 11.7 | 4.4 | 15.7 | 5.1 | <.001*** |
| Spindle-SO % F | 17.9 | 5.6 | 27.3 | 8.6 | 15.1 | 5.8 | <.001*** |
| Spindle-SO % C | 17.9 | 5.6 | 25.2 | 7.1 | 16.2 | 5.6 | <.001*** |
| $PP_{Mean}$ F | 12.7° | 20.1° | 19.5° | 23.5° | 5.6° | 16.6° | 0.010* |
| $PP_{Mean}$ C | 20.9° | 17.2° | 30.9° | 20.6° | 11.8° | 14.9° | <.001*** |
| Upstate% F | 54.64 | 10.72 | 46.32 | 10.36 | 56.18 | 9.83 | <.001*** |
| Upstate% C | 58.00 | 7.50 | 45.97 | 9.13 | 60.56 | 6.6 | <.001*** |

F = frontal. C = central. Spindle density = Spindles per minute, averaged over frontal/central electrodes. SO = Slow oscillations, summed over frontal/central electrodes. SO-spindle%: the percentage of spindles occurring during slow oscillation out of all spindles. Spindle-SO%: the percentage of slow oscillations with a spindle occurrence. NREM: Non-rapid eye movement sleep. N2–3: NREM sleep stage 2 and 3. p = p-value of pairwise t-test comparing N2 and N3 sleep values. *** p < .001; * p < .05. Reproduced with the permission of the copyright holder (Frontiers in Behavioral Neuroscience).

The associations between SO-spindle synchrony and metaphor retention were examined next. MI between the oscillation ranges of 0.2–1.25 Hz (phase frequencies) and 12–16 Hz (amplitude frequencies) was not associated with ΔSleep (p-values > .898). SO–spindle% was associated with ΔSleep in N3 sleep (p-values < .047) but not N2 or NREM combined. Analyses on preferred phase showed robust associations between frontal and central Upstate% and frontal $PP_{Mean}$ (p-values < 0.019) in NREM sleep (Figure 11 B). Additionally, frontal Upstate% was significant when examining N2 and N3 sleep separately (p-values < .046). Including spindle density as an additional covariate did not affect their statistical significance.

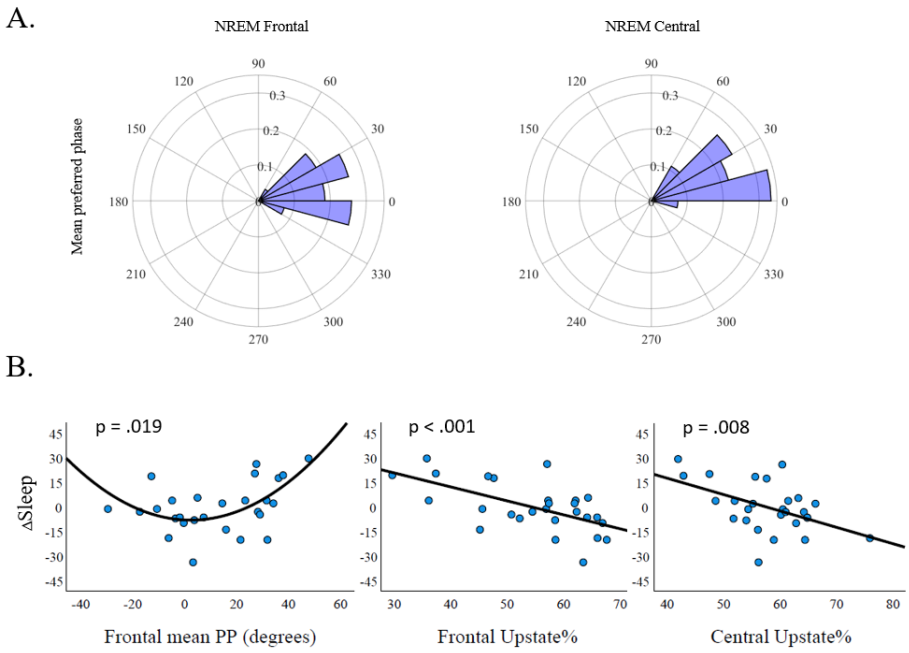


**Figure 11.** Mean preferred phase and memory outcomes. (A) Circular histograms of mean preferred phase angles in a slow oscillation (SO) cycle for frontal and central SO–spindle complexes. The mean angles showed a tendency to cluster at the SO positive peak (i.e. 0°). (B) ΔSleep, representing overnight forgetting, was associated with the frontal mean circular direction (left; p = .019) and with the frontal and central percentage of SO-tied spindles peaking at the SO upstate (±45°) (p < 0.001 and p = .008, respectively). Reproduced with the permission of the copyright holder (Frontiers in Behavioral Neuroscience).

ΔWake did not associate significantly with MI, SO–spindle%, $PP_{Mean}$, or Upstate% in any sleep stage (*p*-values ≥ 0.110). To assess the sleep-specificity of the observed SO-spindle coupling in memory retention, a mixed ANOVA with ΔSleep and ΔWake as within-subject variables was run. The delay condition did not interact with either $PP_{Mean}$ or Upstate% (p-values ≥ 0.135).

Finally, inter-spindle synchrony was studied. The channel-pair-wise grand mean raw PLIs differed from the surrogate significantly (p-values < 0.001, Bonferroni-corrected), denoting that PLI was higher between temporally overlapping spindles than randomly paired spindles. Between different electrode pairs, both PD and cPLI values were significantly different (p-values < .001). PD ranged between 0.237 (F3–C4) and 0.372 (C4–F4), and cPLI ranged between 0.122 (F3–C4) and 0.198 (F3–C3). The channel pair grand means correlated significantly between PD and cPLI ($r$ = 0.773, p = .003), indicating that the probability of propagation between certain electrodes was associated with phase synchrony. However, neither ΔSleep nor ΔWake was associated with PD or cPLI (p-values > .080).

## 5.6 STUDY IV: SLOW OSCILLATION-SPINDLE COUPLING, *BDNF* VAL66MET AND *COMT* VAL158MET

Rayleigh's test showed that both fast and slow spindle peaks were non-uniformly distributed over SO cycle (p-values < .001). The grand mean phases for fast and slow spindles were -24.8° and 84.0°, respectively (Watson-Williams test $p < .001$). RVL was higher for fast, compared to slow, spindles (fast RVL = 0.32 vs. slow RVL = 0.25, $p < .001$). Mean coupling distance was shorter for fast spindles (from 0°) than slow spindles (from 90°), 1.21 rad vs. 1.26 rad, respectively ($t = -3.224$, $p = .002$). Figure 12 A shows the mean phase distribution for frontal fast and slow SO-spindles over the SO cycle.

Recognition accuracy was significantly associated with fast spindle mean coupling distance (from 0°) [$F_{(1, 147)} = 9.522$, $p = .002$] and Upstate# [$F_{(1, 146)} = 6.421$, $p = 0.012$]. Controlling for general cognitive ability, slow oscillation activity or spindle density did not affect the significance statuses regarding coupling distance ($p \leq 0.006$) or Upstate# ($p \leq 0.038$). Slow spindle coupling measures were not significant (p-values $\geq 0.059$). See Figure 12 B for the association between frontal fast SO-spindle coupling and averaged recognition accuracy. Central fast spindle coupling measures were not significantly associated with recognition accuracy (p-values $\geq 0.253$).

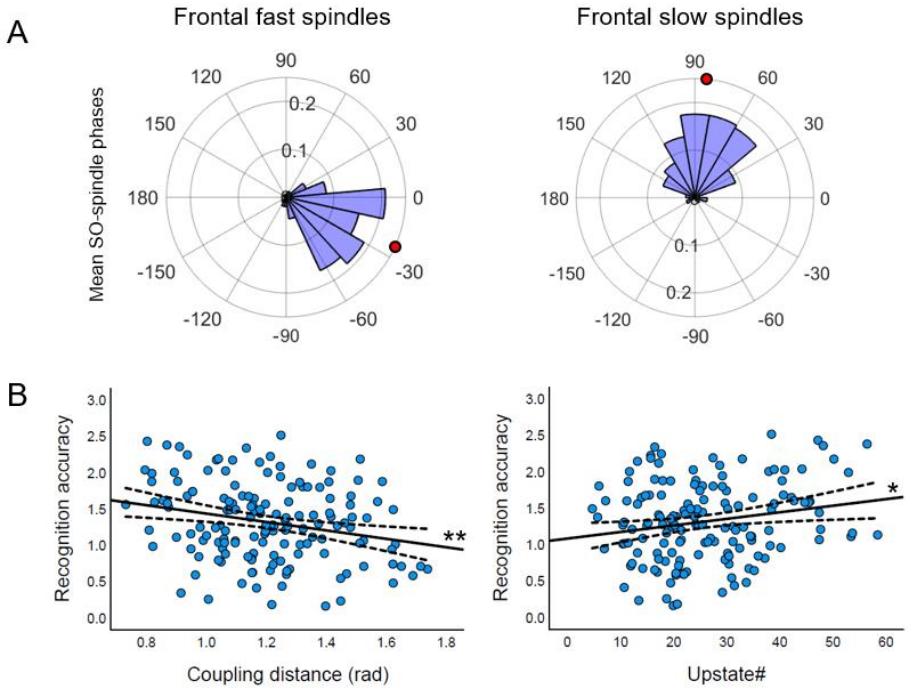


**Figure 12.** Frontal slow oscillation-spindle coupling in the whole sample. (A) Polar histograms illustrate the distribution of participant-wise mean phases on slow oscillation cycle for fast (left) and slow sleep spindles that peak during slow oscillation cycles (SO-spindles). The red dot denotes grand mean phase (-24.8° and 84.0° for fast and slow SO-spindles, respectively). (B) Frontal fast spindle mean coupling distance (in radians) and Upstate# associate significantly with overnight recognition accuracy (p = .002 and p = .012, respectively). Covariates: sex, sleep duration and total time awake. ** p < 0.01. * p < 0.05. Dashed lines represent 95 % confidence intervals. Reproduced with the permission of the copyright holder (Behavioural Brain Research).

Val$_{BDNF}$ homozygotes and Met$_{BDNF}$ carriers did not differ in fast or slow spindle SO-phase distribution (Watson-Williams test p = .841 and p = .438, respectively), RVL [$F_{(1, 151)}$ = 0.021, p = .885 and $F_{(1, 151)}$ = 0.219, p = .641], coupling distance [$F_{(1, 151)}$ = 0.011, p = .917 and $F_{(1, 151)}$ = 0.258, p = .652) or Upstate#/Descending# ($F_{(1, 151)}$ = 2.319, p = .130 and $F_{(1, 151)}$ = 0.710, p = .410]. However, Val66Met moderated the association between recognition accuracy and fast spindle Upstate# [$F_{(1, 144)}$ = 4.669, p = .032] but not coupling distance [$F_{(1, 145)}$ = 0.011, p = .917]. Slow spindle coupling measures did not interact with Val66Met on recognition accuracy (p-values ≥ 0.612).

Within-group follow-up tests revealed that Upstate# associated with recognition accuracy in Val$_{BDNF}$ homozygotes [$F_{(1, 99)}$=12.933, p < 0.001] but not in Met$_{BDNF}$ carriers [$F_{(1, 42)}$ = 0.024, p = .877]. Further exploring bin-wise

associations in Val$_{BDNF}$ homozygotes showed significant associations regarding Bin4 [$F_{(1, 99)} = 9.634$, $p = .002$] and Bin5 [$F_{(1, 99)} = 13.044$, $p < 0.001$], i.e. ±45° from the positive SO peak (0°). Illustrating the bin-wise associations with heat-mapped regression t coefficients show that the proximity of SO upstate relates positively with better memory outcome in Val$_{BDNF}$ homozygotes (Figure 13).

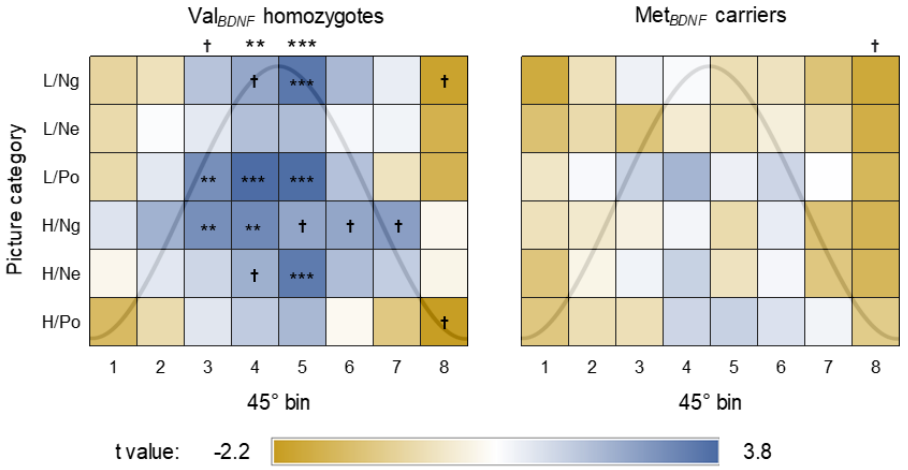


**Figure 13.** Heat-mapped linear regression t values between bin-wise SO-spindle frequencies and recognition accuracies per picture categories (arousal/valence; L=low, H=high, Ng=negative, Ne=neutral, Po=positive). In Val$_{BDNF}$ homozygotes, significant associations accumulate close to the positive slow oscillation peak. The significance of linear mixed model analyses on overall recognition accuracy (averaged across the picture categories) shown above the grid. No significant associations were found in Met$_{BDNF}$ carriers. Covariates: sex, sleep duration and total time awake. *** $p < 0.001$; ** $p < 0.01$. † not significant after the correction for multiple tests. Reproduced with the permission of the copyright holder (Behavioural Brain Research).

*COMT* Val158Met did not associate with fast or slow phase distribution (pair-wise Watson-Williams test $p \geq .302$ and $p \geq .292$, respectively), RVL [$F_{(1, 151)} = 0.392$, $p = .676$ and $F_{(1, 151)} = 2.262$, $p = .108$] or Upstate#/Descending# [$F_{(1, 151)} = 0.110$, $p = .896$ and $F_{(1, 151)} = 0.481$, $p = .619$]. However, coupling distance differed significantly regarding slow [$F_{(1, 151)}=3.209$, $p = .043$] but not fast spindles [$F_{(1, 151)} = 0.557$, $p = .574$]. Slow spindle coupling distance was shortest in Val$_{COMT}$ homozygotes (1.17 rad; Val$_{COMT}$/Met$_{COMT}$: 1.29 rad; Met$_{COMT}$ homozygotes: 1.27 rad), differing significantly from the heterozygotes ($p = .039$, Bonferroni-corrected). No significant interactions between Val158Met and SO-spindle coupling measures on recognition accuracy were found regarding either fast (p-values ≥ 0.886) or slow (p-values ≥ 0.768) SO-spindles.

Investigating in the whole sample whether picture valence or arousal interacted with fast spindle coupling measures showed a significant interaction between Upstate# and valence [$F_{(2, 292)} = 3.345$, $p = .037$] but not arousal ($p = .733$). Recognition accuracy difference scores between the valence categories were created, i.e. Positive–Neutral, Negative–Neutral and Positive–Negative. Linear regression test was significant between Upstate# and Positive–Neutral ($t = 2.594$, $p = .010$) (Figure 14) but not regarding Negative–Neutral ($p = .277$) or Positive–Negative ($p = .150$).

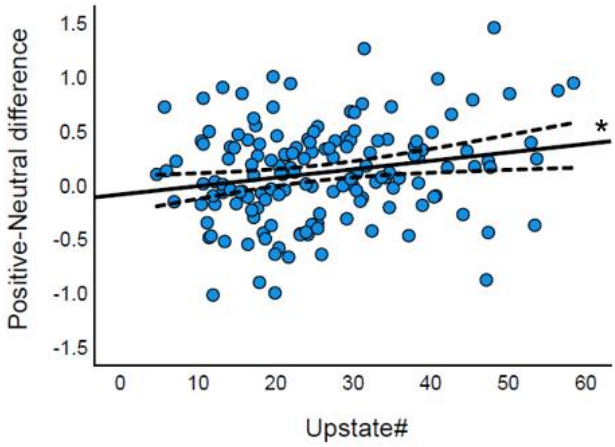


**Figure 14.** Upstate# associates with the difference between positive and neutral recognition accuracy ($p = .010$). Covariates: sex, sleep duration and total time awake. * $p < 0.05$. Dashed lines represent 95 % confidence interval. Reproduced with the permission of the copyright holder (Behavioural Brain Research).

Three-way 'genotype x SO-spindle measure x arousal/valence' interactions were not significant regarding Val66Met (p-values ≥ 0.169) or Val158Met (p-values ≥ 0.096).

## 5.7 SUPPLEMENTARY ANALYSIS: *BDNF* VAL66MET, HIT RATE AND FALSE ALARM RATE

Recognition accuracy, defined as *d'*, consists of the difference between the probabilities to correctly recognize target items (i.e. Hit Rate) and to incorrectly recognize sham items (i.e. False Rate). The Studies I, II and IV in this thesis reported that *BDNF* Val66Met moderated the associations between recognition accuracy and sleep spindle density/SO-coupling (Studies I and IV) or sleep proportion during the retention period (Study II). However, it remains undefined whether these measures contribute on recognition accuracy via both Hit Rate and False Rate, or if their impact on recognition accuracy is tied more strongly with one component over the other.

To explore the issue, mixed ANOVA models to explore the issue were created. Instead of deploying recognition accuracy scores as dependent variable, separate models for Hit Rate and False Rate were used, each consisting of two levels of arousal and three levels of valence (as in the main analyses). *BDNF* Val66Met was assigned as between-subjects variable and either Sleep% (Study II; the percentage of sleep during the retention period) or Upstate# (Study IV; the number of fast spindles occurring within ±45° from the positive slow oscillation peak) as independent continuous predictor. An interaction term 'Val66Met x Sleep%', or 'Val66Met x Upstate#' was tested in their respective models. Sex was assigned as covariate in the analyses regarding Sleep% whereas also sleep duration and the time spent awake were controlled for in the analyses regarding Upstate#.

Hit Rate as the dependent variable, Val66Met interacted significantly with Upstate# ($F = 13.991$, $p < .001$) but not with Sleep% ($F = 0.045$, $p = .833$). Follow-up regression tests separately for the genotypic subgroups showed that Upstate# associated significantly with Hit Rate (averaged over picture categories) in $Val_{BDNF}$ homozygotes ($t = 4.975$, $p < .001$) but not in $Met_{BDNF}$ carriers ($t = -1.206$, $p = .234$). Next, examining False Rate revealed a significant interaction between Val66Met and Sleep% ($F = 13.950$, $p < .001$) but not Upstate# ($F = 1.766$, $p = .186$). Regression tests indicated that Sleep% associated negatively with False Rate (averaged over picture categories) in $Val_{BDNF}$ homozygotes ($t = -3.011$, $p = .003$) and positively in $Met_{BDNF}$ carriers ($t = 2.169$, $p = .035$). Figure 15 illustrates the regression slopes for Hit Rate and Upstate# (A) and False Rate and Sleep% (B).

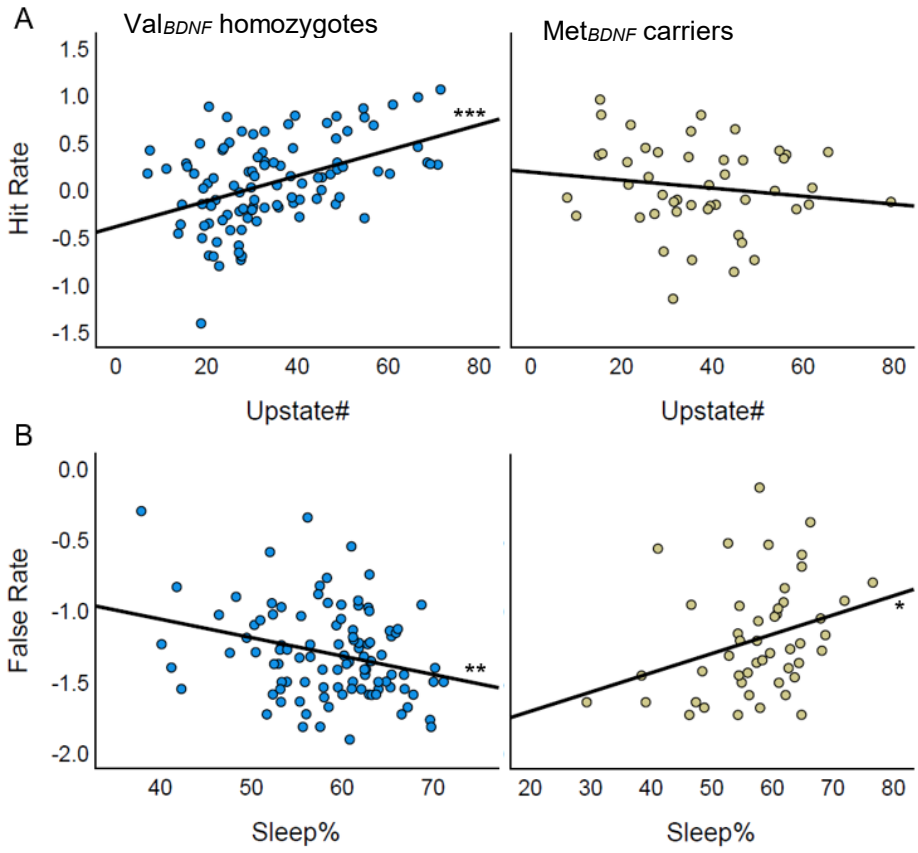


**Figure 15.** Hit rate, false alarm rate and *BDNF* Val66Met. *BDNF* Val66Met moderates the associations between Upstate# and Hit Rate ($p < .001$), as well as between Sleep% and False Rate ($p < .001$). (A) A strong positive association is seen in Val$_{BDNF}$ homozygotes between Upstate# and Hit Rate ($p < .001$). (B) Sleep% associates negatively in Val$_{BDNF}$ homozygotes ($p = .003$) and positively in Met$_{BDNF}$ carriers ($p = .035$). *** $p < .001$. ** $p < .01$. * $p < .05$.

# 6 DISCUSSION

## 6.1 MEMORY OUTCOME IS ASSOCIATED WITH SLEEP SPINDLES AND SLOW OSCILLATION-SPINDLE COUPLING

The involvement of sleep spindles in memory consolidation during sleep is well-documented. Sleep spindles are implicated with the potency for LTP induction (Rosanova & Ulrich, 2005) and they also play a vital part in off-line memory reactivation (Ngo, Fell, & Staresina, 2020). Numerous studies have reported associations between sleep spindles and memory outcome (Clemens et al., 2005; Gais et al., 2002; Genzel et al., 2009; Göder et al., 2015; Ruch et al., 2012; van der Helm et al., 2011), and these findings were augmented by Studies I, III and IV in this thesis. In the sample consisting of 17 y old adolescents from the Glaku cohort, the densities of frontal fast and slow sleep spindles were associated with overnight picture recognition accuracy. Controlling for general cognitive ability did not have any major impact on the associations, dispelling a possible contribution of intelligence (Bódizs et al., 2005; Fogel & Smith, 2011; Schabus et al., 2006; Schabus et al., 2008) on the observed relation between spindles and memory outcome. Interestingly, these positive associations were confined to N2 spindles only, contradicting with the view that spindle-related memory consolidation is SWS-specific (Cox et al., 2012). However, the pattern where sleep spindles during N2, but not N3, sleep correlate with memory performance has been brought up previously (Ruch et al., 2012; van der Helm et al., 2011), which suggests them being a relevant indicator, or a mechanism, for memory consolidation over sleep.

Examining spindle activity during SWS necessitates considering slow oscillations and their synchronization with sleep spindles. Especially fast sleep spindles that occur during the positive SO phase (i.e. upstate) of high neuronal responsivity (Chauvette et al., 2012) have been under increasing focus in recent human sleep-memory research. Previous reports (Hahn et al., 2020; Helfrich et al., 2018; Mikutta et al., 2019; Muehlroth et al., 2019) on the topic were now complemented by the observations in this thesis (Studies III and IV), as the tendency for spindles to peak close to the SO positive peak correlated positively with overnight performance in both verbal and visual memory tasks. The test statistics were stronger regarding the cued metaphor recall than picture recognition. This aligns with the evidence that sleep's benefit on memory outcome is higher in recall-type tasks, relative to recognition (Berres & Erdfelder, 2021; Lipinska et al., 2019), and when measuring pre- to post-sleep difference instead of delayed retrieval only (Berres & Erdfelder, 2021). Nevertheless, this thesis supports the conception that fast spindles coinciding with SO upstate cause a particularly strong calcium influx into pyramidal

neurons and thus form a potent window for memory consolidation (Niethard, Ngo, Ehrlich, & Born, 2018). The most robust associations were seen when investigating NREM (N2+N3) sleep in combination. While separate examinations of N2 and N3 sleep showed more precise coupling during N3 sleep, similar dynamics in SO-spindle coupling and memory applied for both stages.

Regarding the operationalization of SO-spindle coupling, two methodological factors should be noted. First, the synchrony between SOs and sleep spindles can be operationalized by the means of cross-frequency coupling or by examining it in an event-based manner. The former refers to an approach where the relation between the amplitude frequency (spindle range, in this case) and phase frequency (i.e. SO range) is investigated. That is, how is spindle amplitude modulated by the phase angle in the SO frequency band, regardless of any detectable events within those bands. While this approach may readily show a strong general modulation by SO frequencies on spindle amplitude (Mikutta et al., 2019), it appears that better indicator for declarative memory consolidation is an event-based approach, i.e. where only events (SOs spindles or both) conforming to certain detection thresholds are considered consequential. This was indeed examined in this thesis, and overnight metaphor retention was significantly predicted by event-based SO-spindle coupling but not modulation index (Tort et al., 2010), the pattern paralleling a previous report (Mikutta et al., 2019). The significance of SO upstate in spindle-related memory consolidation is likely linked to a specific sequence of excitatory and inhibitory inputs during SO-upstate-nested spindles, resulting in elevated neuronal calcium activity in comparison with isolated SO or spindle events (Niethard et al., 2018). Such a state of optimal synaptic plasticity is not necessarily captured in modulation index, which is not tied to specific events.

The second consideration concerns whether event-based SO-spindle coupling is examined in relative or absolute terms. Relative measures of SO-spindle coupling include resultant vector length (Helfrich et al., 2018), mean SO angle at spindle peaks (Mikutta et al., 2019), mean circular distance from the positive SO peak (Hahn et al., 2020) or the percentage of SO-coupled spindles (Denis et al., 2020). These relative measures disregard the total amount of the supposedly mechanistically consequential events and may a rather mirror the neurostructural characteristics coordinating the timing of the synchrony (Muehlroth et al., 2019). Within this thesis, both relative and absolute measures were used, albeit the latter only regarding picture recognition. It was found that both approaches yielded significant associations when the examination concerned the entire samples. However, it is possible that inter-individually variable propensity for neuronal plasticity could favor one approach over other. This topic is discussed in detail in Chapter 6.2.

It is well-established that the oscillatory synchrony between sleep spindles and SOs are involved in memory retention over sleep. However, sleep spindles also show a non-random tendency to overlap temporally between different electrode locations (Frauscher et al., 2015; O'Reilly & Nielsen, 2014; Piantoni et al., 2017; Souza et al., 2016), and moreover, to gravitate rapidly towards phasic synchrony between the simultaneous spindles (Souza et al., 2016). Study III examined the probability for a (seed) spindle to be overlapped by another spindle and found highest probabilities for temporal overlap between the electrode pairs within hemisphere (e.g. C4–F4). This was paralleled by resembling patterns in electrode pair-wise PLI values (Stam et al., 2007), a measure of phase synchrony. PLI was also markedly higher between simultaneous spindles, in contrast to random spindle pairs used as surrogates. However, even though temporal and phasic *inter-spindle synchrony* was observed, neither had any associations with memory retention scores, be it over a delay containing sleep or wake. The finding seems to contrast with previous theoretical and experimental work. Indeed, it has been speculated whether simultaneous 'matrix' spindles would serve the consolidation of widespread memory representation (novel metaphors in this case) (Piantoni et al., 2016). Synchronized neuronal firing during waking seems to underlie different forms of cognitive processes (Mizuhara & Yamaguchi, 2007; J. M. Palva et al., 2010; Rutishauser et al., 2010; Schack & Weiss, 2005), and oscillatory coherence between distinct brain areas during sleep (including spindle range) has been shown to increase by pre-sleep learning (Mölle et al., 2004). The nature of sleep spindles as facilitators of local plasticity (Genzel, Kroes, Dresler, & Battaglia, 2014) questions whether their globalization serves any activity-dependent need or, rather, mirrors the cortical state and cortico-thalamocortical properties (Fernandez & Lüthi, 2020), irrespective of memory function. However, the used fronto-central EEG montage was limited in terms of thoroughly investigating spindle propagation characteristics. Also temporal and parietal areas have been implicated with propagated spindles (Piantoni et al., 2017) or learning-related sleep EEG coherence (Mölle et al., 2004). Hence, conducting a wider-scale EEG would provide more representative results.

What is the role of slow spindles in memory outcome? Regarding the coupling with SOs, Study IV found slow spindles to accumulate during the downward slope of SOs, as previously reported (Muehlroth et al., 2019; Mölle et al., 2011). However, their coupling did not associate with memory outcome. A previous study (Muehlroth et al., 2019) reported a negative association between the retention of scene-word pairs and slow spindle activity during the up- to downstate transition. The authors proposed such a coupling pattern, along with misaligned fast SO-spindle coupling, be characteristic of 'aged' brain. On the other hand, another study (Mölle et al., 2011) found SO-coupled fast and slow spindles to occur in coordinated fashion, upstate-tied fast spindles being followed by slow spindles during the up-to-down-state

transition. The authors suggested slow spindles being associated in cortico-cortical interaction. This speculation gains interest from Study I, where the density of frontal slow spindles (regardless of coupling) during N2 sleep correlated positively with memory outcome. Provided that cortico-cortical connectivity is enhanced during light sleep (Genzel et al., 2014), the found association could indeed be explained via widespread cortical processing during slow spindles. However, being unable to dispel other viable factors, like (pre-sleep) learning aptitude (Hoedlmoser et al., 2014; Schabus et al., 2006; Studte, Bridger, & Mecklinger, 2015), the issue remains unresolved.

Few studies have inspected how sleep spindles or their SO-coupling predict memory retention over *wake*. In Study III, such examination did not yield significant findings. However, these loose associations paralleled the ones observed in the sleep condition, and subsequently, the associations between the delay conditions did not differ significantly. Thus, the presumed benefit from precise SO-spindle coupling may not be fully sleep-specific. One possibility is that coupling measures reflect neural properties like gray matter integrity in medial frontal areas (Helfrich et al., 2018) which, in turn, influence trait-like cognitive capabilities (Ohtani et al., 2014) supporting mnemonic functions. Studies I and IV did not find general cognitive abilities to be of major relevance regarding oscillatory properties or their relation with overnight memory outcome, although generalizing these findings to wake-time retention necessitates caution. Another reason for the non-significant difference between the delay conditions may relate to the properties of the study. For example, some participants in the sample neared the ceiling in sleep-containing retention, narrowing the variance and thus limiting the resolution of sleep-specificity.

Taken together, evidence was obtained for the involvement of especially fast sleep spindles on memory retention in this thesis. In accordance to recent human experiments, the coupling of fast spindles with neocortical SOs was seen a significant predictor of overnight memory performance. Their preferential peaking during the depolarized SO upstate associated with both visual recognition and verbal cued recall. Notably, this impact was confined to event-based examination of sleep spindles and SOs, whereas the general modulation between phase and amplitude did not yield significant results. The temporal or phasic synchrony between spindles in different cortical areas did not appear consequential regarding memory consolidation, underscoring specific importance of SO-upstate-coupled fast sleep spindles.

## 6.2 MODERATION BY VAL66MET AND VAL158MET ON SLEEP SPINDLES, SO-SPINDLE COUPLING AND MEMORY OUTCOME

The described mechanisms and well-established significance of sleep spindles on memory consolidation made it compelling to investigate the possible moderation by plasticity genes. The gene variants of interest were *BDNF* Val66Met and *COMT* Val158Met, whose documented associations on neural anatomy (Honea et al., 2009; S. N. Kim et al., 2013; Molendijk et al., 2012; Montag et al., 2009; Pezawas et al., 2004; Tian et al., 2013), activation (Bertolino et al., 2006; Egan et al., 2003; Schofield et al., 2009), sleep homeostasis (Bachmann et al., 2012; Goel et al., 2011) and memory function (Bertolino et al., 2006; de Frias et al., 2004; Krach et al., 2010; Toh et al., 2018) warranted assuming a moderation on overnight learning and/or its mechanisms.

*BDNF* Val66Met has received considerable interest in memory research. $Val_{BDNF}$ homozygosity is commonly linked with improved memory performance over $Met_{BDNF}$ carriers (Toh et al., 2018). Some studies examining memory retention over sleep have reported better performance in $Val_{BDNF}$ homozygotes relative to $Met_{BDNF}$ carriers regarding positive words (Cathomas et al., 2010) and neutral faces (Mascetti et al., 2013). However, this thesis found no difference in overall recognition accuracy according to the *BDNF* genotype (Study II), which converges with an earlier study deploying pictures of varying emotionality (Harrington et al., 2019). It may be that the type of material modulates any subtle influences of Val66Met on overnight recognition.

Investigating mechanisms may provide insight beyond outright performance. Studies examining the interaction between sleep-dependent consolidation mechanisms and Val66Met are scarce, yet one report showed slow oscillation power to benefit specifically $Val_{BDNF}$ homozygotes (Mascetti et al., 2013). The Studies I and IV contributed to the topic by scrutinizing spindle density and SO-spindle coupling, respectively. Regarding the former, it was found that the density of fast spindles during N2 sleep associated positively with overnight picture recognition accuracy in $Val_{BDNF}$ homozygotes, whereas this relation was not seen in $Met_{BDNF}$ carriers. The significant interaction propelled to ask if Val66Met influences the synchrony between sleep spindles and SOs. Indeed, as the synchrony is reportedly prefrontally orchestrated (Helfrich et al., 2019) and dependent on connectivity characteristics (Weaver et al., 2016), Val66Met with its reported implications on these properties (Fera et al., 2013; Thomason, Yoo, Glover, & Gotlib, 2009; Wei et al., 2012) could also relate with SO-spindle synchronization constancy.

In Study IV, it turned out that the alignment of sleep spindles on SO cycle did not differ between Val$_{BDNF}$ homozygotes and Met$_{BDNF}$ carriers. Instead, Val66Met moderated the associations between SO-spindle coupling and recognition accuracy, such that SO-upstate-coupled fast spindles seemed to benefit only Val$_{BDNF}$ homozygotes. Markedly, this interaction was observed when examining the absolute, but not relative, measures of coupled spindles. That is, the amount of presumably potentiating events induced a significant difference between the genotypes, implying that the event itself is more consequential in Val$_{BDNF}$ homozygotes. The mechanism may relate to the enhancing impact of BDNF on NMDAR function (Caldeira et al., 2007). NMDARs are involved in triggering the calcium influx during spindles, which consequently results in signaling cascades underlying LTP (Lindemann et al., 2016). Accordingly, carrying Met$_{BDNF}$ alleles may relatively limit NMDAR-dependent plasticity (Ninan et al., 2010). Converse logic is possible, too. Val66Met affects the activity-dependent release of BDNF (Z.-Y. Chen et al., 2004) and sleep spindles have been proposed a physiological trigger for BDNF release (Yang et al., 2016). Hence, the abundance of spindles may result in higher BDNF tone in especially Val$_{BDNF}$ homozygotes during spindle-rich episodes, thus contributing on LTP stabilization (Lu et al., 2011; Panja & Bramham, 2014).

Recognition accuracy is a measure consisting of both correctly recognized target items and incorrectly recognized sham items. Accordingly, it was explored whether the moderation by *BDNF* Val66Met concerned equally both elements or only one of them. In the supplementary analyses it turned out that specifically the correct recognition of target pictures was predicted by SO-upstate-coupled spindles in Val$_{BDNF}$ homozygotes. The finding appears consistent with the reasoning that numerous potentiating events in Val$_{BDNF}$ homozygotes would strengthen the existing (i.e. true) memory traces and result in efficient recognition of previously seen stimuli. While no previous study, to the best of the current knowledge, has directly examined the topic, converging evidence links sleep spindles with lower number of verbal false memories (Kuula et al., 2019). In another study, *BDNF* Val66Met did not relate with overall verbal recognition memory performance, but hit rate for correct items deteriorated more strongly in Met$_{BDNF}$ carriers during a week's delay (Montag et al., 2014). The authors suspected poorer memory consolidation in Met$_{BDNF}$ carriers, perchance here reflected in the dynamics between (SO-coupled) sleep spindles and the correct recognition of target pictures.

A factor that possibly contributes to the lack of spindle-related memory associations in Met$_{BDNF}$ carriers concerns white matter tracts. Met$_{BDNF}$ allele is implicated with comparatively higher anatomical connectivity (Chiang et al., 2011; Tost et al., 2013; Ziegler et al., 2013) which has been explained by more inefficient pruning of silent axons, relative to Val$_{BDNF}$ homozygotes (Ziegler et

al., 2013). Some studies have found that cognitive performance associates with white matter diffusion properties only in $Val_{BDNF}$ homozygotes (Chiang et al., 2011; Huang et al., 2014). This pattern resembles the Val66Met-moderation found in this thesis and becomes especially interesting considering that white matter integrity underlies the propagation of sleep spindles (Gaudreault et al., 2018; Piantoni et al., 2013) and their impact on learning (Mander et al., 2017). While it would be premature to suspect that sleep spindles would be inconsequential for learning in $Met_{BDNF}$ carriers, the association may not be evidently dose-dependent.

*COMT* Val158Met was also examined regarding SO-spindle coupling and overnight recognition accuracy. Val158Met did not associate with overall recognition accuracy (Study II), complementing previous – mixed – observations from non-sleep studies on recognition memory (Bertolino et al., 2006; de Frias et al., 2004; Krach et al., 2010). Moreover, Val158Met did not interact with SO-spindle coupling on recognition memory (Study IV). This suggests that *COMT* and its implications on prefrontal (J. Chen et al., 2004) or hippocampal (Laatikainen, Sharp, Bannerman, Harrison, & Tunbridge, 2012) dopamine, and subsequently, synaptic plasticity (Otani, Bai, & Blot, 2015; Otani et al., 2003) do not affect the propensity for spindle-related memory consolidation. Thus, it may be that the possible influence of *COMT*, and consequently, dopamine, on the spindle-memory-relation does not emerge without changes in spindle measures. Some studies suggest that dopamine levels may have a direct impact on spindle characteristics. A previous study reported higher fast spindle density along $Met_{COMT}$ alleles (Schilling et al., 2018). Additionally, pharmacologically elevating nocturnal dopamine levels has been reported to alter SO-spindle dynamics and result in accelerated forgetting of weakly encoded words (Isotalus, 2020). In Study IV, the density and SO-coupling of fast spindles did not differ according to *COMT* genotype, possibly explaining why no memory outcome differences were observed, either. However, $Val_{COMT}$ homozygotes showed shortest coupling distance for slow spindles (±45 from the up- to downstate transition at 90°) where slow spindles generally accumulate. This suggests that neuroanatomical or functional differences exerted by Val158Met has an influence on frontal SO-triggered slow spindles. This did not reflect any learning implications, as the coupling of slow spindles and SOs was not predictive of memory outcome.

In sum, the association between sleep spindles and overnight recognition accuracy was moderated by Val66Met. The assumed influence of Val66Met on activity-dependent BDNF secretion (Z.-Y. Chen et al., 2004) may thus intensify the impact of spindles, due to BDNF's reported effects on LTP (Ninan et al., 2010) and cellular calcium dynamics (Caldeira et al., 2007). However, this speculation posits that the associations reflected mechanistic sleep consolidation. Alternatively, successful pre-sleep learning can augment SO depolarizations (Mölle et al., 2011), increase spindle activity (Gais et al., 2002;

Morin et al., 2008) and modulate fast spindle coupling (Mölle et al., 2009; Yordanova et al., 2017). Hence, the increased coupling seen in high-performing participants (across the whole sample and in $Val_{BDNF}$ homozygotes) could result from more efficient encoding. This effect would be emphasized in $Val_{BDNF}$ homozygotes (Alonso et al., 2002; Ninan et al., 2010) and reflected by enhanced SO-spindle coupling. However, this contrasts the evidence where Val66Met-driven changes specifically emerge after sleep (Cathomas et al., 2010; Mascetti et al., 2013). No interactions were seen regarding *COMT* Val158Met. It may be that similar effects on synaptic plasticity that were speculated regarding BDNF do not concern dopaminergic plasticity. Age may be a factor here, as it interacts with Val158Met in terms of dopamine levels (Wahlstrom, White, & Luciana, 2010) and neural connectivity (Meyer et al., 2016). Hence, in the adolescent sample, the implications of $Met_{COMT}$ alleles on sleep-dependent memory consolidation may well diverge from what would be found from adults.

## 6.3 SLEEP-TO-WAKE RATIO, GENOTYPIC MODERATION AND MEMORY OUTCOME

Study II examined if the temporal distribution of sleep and wake between memory encoding and retrieval affected overnight picture recognition accuracy. The in-home sleep measurement without imposing sleep schedules aimed at preserving natural homeostatic process of the adolescent participants, at the same time providing high variability in sleep timing. Specifically it was asked if the relation between sleep/wake and memory outcome was moderated by *BDNF* Val66Met or *COMT* Val158Met. Indeed, a moderation by Val66Met was found such that higher proportional sleep associated positively with memory outcome in $Val_{BDNF}$ homozygotes only.

The significant interaction between sleep percentage and Val66Met begs the question whether it merely reflects the findings already discussed – that is, memory benefit from sleep percentage in $Val_{BDNF}$ homozygotes being a consequence of spindle activity. However, the association between sleep percentage and recognition accuracy appeared to be drawn by the performance impairment along prolonged wake, rather than any benefit by total sleep duration or by the time spent in SWS or REM sleep. Possible mechanisms are speculative at this stage. One explanation concerns sleep pressure, which has been suggested to accumulate more rapidly in $Val_{BDNF}$ homozygotes relative to $Met_{BDNF}$ carriers, reflected in higher slow-wave activity (Bachmann et al., 2012). The time spent awake after encoding increases sleep pressure which potentially impairs LTP maintenance (Prince & Abel, 2013) and reduces signal-to-noise ratios of memories (Tononi & Cirelli, 2014). During the subsequent sleep, the selective downscaling of synaptic weights (Tononi & Cirelli, 2014) could obviate memories with

weakened relative strength. It was indeed observed that accumulated wake before sleep onset related with poorer performance in $Val_{BDNF}$ homozygotes. No association was observed regarding the wake in the morning.

Sleep quality may interact with Val66Met specifically on *post-sleep* memory function. One study with middle-aged and older participants reported consolidated sleep to benefit $Val_{BDNF}$ homozygotes in post-sleep memory tasks (including both encoding and retrieval), whereas the relation was even opposite in $Met_{BDNF}$ carriers (Gosselin et al., 2016). The authors proposed that hippocampal strategy, favored by $Val_{BDNF}$ homozygotes, was more dependent on sleep than the striatal strategy deployed by sleep-deprived $Met_{BDNF}$ carriers. The supplementary analysis in this thesis found the Val66Met-moderated effect of sleep proportion concerning specifically false alarm rate, i.e. incorrect recognitions of foil pictures: higher sleep percentage decreased false recognitions in $Val_{BDNF}$ homozygotes but increased them in $Met_{BDNF}$ carriers. Striatal function has been observed to associate with old/new recognition judgements (Scimeca & Badre, 2012) and proposed to underlie Val66Met-moderation in go/no-go response inhibition. Given that the recognition task in Studies I, II and IV deployed a go/no-go paradigm, it becomes tempting to propose striatal contribution on the interaction between Val66Met and (lack of) sleep on false recognition. However, this speculation is based on methodologically distant evidence, necessitating further research to clarify how the ratio or timing of sleep and wake interacts with *BDNF* Val66Met.

COMT Val158Met did not interact with the variation of sleep/wake on picture recognition memory. This finding complements previous studies that have investigated executive function as the outcome measure from manipulated sleep. These studies have demonstrated detriments after total (Satterfield et al., 2018), but not partial (Goel et al., 2011), sleep deprivation in the carriers of $Val_{COMT}$ allele. Our study did not include induced sleep deprivation and all participants slept at least a few hours during the study night. It may be that more intense, systematic deprivation is required to elicit observable effects.

Finally, it should be noted that sleep percentage during the retention period was not significantly associated with recognition accuracy in the whole sample, contradicting with previous studies reporting adverse effect of prolonged post-encoding wake on picture recognition (Payne, Chambers, & Kensinger, 2012a; Wagner et al., 2007). However, the performance in the simple recognition task may have been less vulnerable to reduced sleep, compared to a more complex task (Kopasz et al., 2010). Also, the ratio of wake and sleep in the sample approximated the habitual sleep patterns of the participants without total sleep deprivation. Even a short sleep may benefit learning (Lahl et al., 2008; Tucker & Fishbein, 2009), and such benefits were likely achieved across the sample.

## 6.4 THE ROLE OF EMOTION AND MATERIAL DIFFICULTY ON OVERNIGHT LEARNING

The selectivity of sleep-dependent memory consolidation is a topic of keen interest but also debate. The theoretical basis of such selectivity leans upon the 'tagging' of salient – e.g. by top-down control or emotional value – memories during encoding for prioritized strengthening during sleep (Bergado et al., 2011). In the adolescent Glaku cohort, markedly higher picture recognition accuracy was seen for emotional, compared to neutral, pictures (Study II). Merging well with previous research (Atienza & Cantero, 2008; Baran et al., 2012; Bennion, Mickley Steinmetz, Kensinger, & Payne, 2013; Harrington, Nedberge, & Durrant, 2018; Hu, Stylos-Allan, & Walker, 2006; B. J. Jones, Schultz, Adams, Baran, & Spencer, 2016; Morgenthaler et al., 2014; Payne et al., 2012a) recognition accuracy was higher for exciting over calm pictures, and for emotionally valenced (negative and positive) over neutral pictures. The interaction of arousal and valence resulted in highest accuracy in arousing negative pictures, in accordance to previous studies (Baran et al., 2012; Bennion et al., 2013; B. J. Jones et al., 2016; Payne & Kensinger, 2011), but additionally in calm positive pictures. Such pictures evoke similar amygdala connectivity than aversive ones (Mickley Steinmetz, Addis, & Kensinger, 2010), perchance reflected by the observed pattern of recognition accuracy. While these results imply sleep-related selectivity, systematic efforts scrutinizing the topic have failed to cement the view that specifically sleep, rather than wake, would prioritize emotional memories (Davidson et al., 2021; Lipinska et al., 2019; Schäfer et al., 2020). Unfortunately, lacking a wake-condition in picture recognition prevents from direct comparison within the thesis.

The phenomenon can be approached by examining the related sleep correlates. First, the duration of sleep, wake, SWS or REM sleep did not interact with the emotional strength on picture recognition (Study II). This is notable in the sense that especially REM sleep has theoretical basis for emotional processing (Walker & van der Helm, 2009), and moreover, evidence from split-night experiments indicate that post-encoding REM sleep, rather than SWS, may improve emotional memory performance (Schäfer et al., 2020). However, this effect is not visible when examining whole night of sleep. It has thus been proposed that e.g. circadian factors may contribute to the findings from split-night designs, or that any possible effect of REM sleep is not dose-dependent and reached with even a short duration of REM sleep (Davidson et al., 2021). Hence, it may be that a linear association between REM duration and emotional selectivity are not readily perceivable without direct manipulations.

In Study IV, however, an interaction between SO-spindle coupling and emotional valence was seen: the higher the amount of SO-upstate-coupled fast

spindles during NREM sleep, the better were positive pictures recognized in comparison to neutral pictures. The finding converges with previous studies that link spindle activity with affective selectivity (Cairney et al., 2014; Kaestner et al., 2013). Interestingly, one study reported higher percentage of SO-coupled spindles to associate negatively with the emotional picture recognition, but only in those participants that underwent stress-induction before memory encoding (Denis et al., 2020). This suggests that a transient condition can modulate how sleep-dependent mechanisms process emotional memories, which likely explains a part of the inconsistencies regarding sleep and emotional selectivity. Nevertheless, more research on how SO-spindle coupling contributes to selective consolidation is warranted.

The genotypic moderators were examined for interactions regarding emotional selectivity in Study II and IV. Regarding *BDNF* Val66Met, no interaction with picture category was found. While this contrasts an earlier study where only $Met_{BDNF}$ carriers showed elevated emotional preference (Harrington et al., 2019), some methodological differences are obvious: the categorization of pictures between these studies was different, and overly aversive pictures were not used in our study due to the adolescent sample. Additionally, no separation was done between 'familiarity' and 'recollection' responses, which possibly attenuated genotypic differences regarding hippocampal contribution (Yonelinas, Aly, Wang, & Koen, 2010). *COMT* Val158Met, on the other hand, interacted with arousal: $Met_{COMT}$ homozygotes showed elevated accuracy for high arousal (over calm) pictures. This diverges from previous reports on adult males, where memory (benefit) for highly arousing items was impaired in $Met_{COMT}$ homozygotes (Gibbs et al., 2014; Naudts et al., 2012). As brought up previously, age may partially explain this discrepancy. During adolescence, $Met_{COMT}$ allele is in a dose-dependent relation with prefrontal dopamine levels (Wahlstrom et al., 2010), cortical thickness (Raznahan et al., 2011) and default mode network connectivity (Meyer et al., 2016), but these associations get inverted by adulthood. Assumedly, this maturational shift could alter the limbic contribution on mnemonic tasks.

Finally, a different approach on selectivity was examined in Study III. The influence of item difficulty on retention was scrutinized, basing on the normative difficulty levels of the memorized novel metaphors (Herkman & Service, 2008). Some studies suggest that sleep-related benefit is greater for semantically unrelated than related word pairs (Payne et al., 2012a), paralleled by reports that sleep spindles are specifically involved in the consolidation of difficult (Schmidt et al., 2006) or weakly-encoded (Denis et al., 2021) material. Notably, the design in Study III allowed comparing whether the delay condition, i.e. wake or sleep, interacted with the difficulty level. First, it was found that the normative difficulty level of the metaphors affected the

probability of successful recall – as expected, more difficult metaphors were less likely retrieved successfully. However, this association was similar across sleep and wake, meaning that sleep did not differ from waking in prioritizing the preservation of difficult metaphorical associations over more easily processed ones. Studies deploying word-pair retention tasks with semantically related and unrelated associations have provided mixed findings. While one study found an interaction between 12-h delay conditions (sleep/wake) and semantic relatedness (Payne et al., 2012a) another report (Lo, Dijk, & Groeger, 2014) presented a pattern where the relative memory performance between wake and sleep was similar regardless of the delay condition. Supposedly the novelty in the metaphoric associations in Study III, and the instructed encoding strategy (i.e. to form a mental image of the metaphors, instead of instructing the participants to "learn" them, as in the studies above) minimized the dependence on previous knowledge in memorizing. This may have equalized inter-item sleep dependency (Schmidt et al., 2006), making the difference between wake and sleep constant.

Taken together, this thesis provides evidence that SO-coupled fast spindles associate more strongly with the retrieval emotional, relative to neutral, memories. While the study design does not permit causal deductions nor direct comparison of retention over sleep and wake, the finding increases the understanding of the involved mechanisms. Indeed, there is accumulating evidence that emotional memory is not solely dependent on REM sleep, and experimental research on the cyclic interplay between NREM and REM sleep is necessary to unravel the dynamic nature of emotional memory consolidation.

## 6.5 METHODOLOGICAL CONSIDERATIONS

### 6.5.1 NATURAL SLEEP

In Studies I, II and IV, the sleep measurements were conducted at the adolescent participants' homes. Fixed sleep schedules were not imposed, but the adherence to the habitual sleep rhythms was endorsed. By this approach, the natural homeostatic and circadian processes of the participants were preserved, which likely enabled non-hindered cognitive functioning (Maire, Reichert, & Schmidt, 2013) and representative sleep structure and EEG characteristics (Bódizs et al.; Dijk & Cajochen, 1997; Dijk & Czeisler, 1995). This also provided a wide variation in wakefulness and sleep, enabling to investigate whether such a spectrum was associated with behavioral outcome. On the other hand, by not imposing schedules for sleep and the subsequent memory test in the morning introduces potential confounders, including

differences in the lengths of pre-encoding wake or retention period. To an extent, their effects can be, and were, statistically controlled for.

### 6.5.2 AGE

The two samples studied in this thesis consisted of ~17 y old adolescents (Studies I, II and IV) or adults aged 22 years on the average (Study III). In both samples, SO-spindle coupling was predictive of memory outcome, conforming to findings from previous studies conducted on adults (Helfrich et al., 2018; Mikutta et al., 2019; Muehlroth et al., 2019). Especially the results found in adolescents necessitate further deliberation, as the age that bridges childhood and adulthood is a period known for ongoing neural maturation (Gogtay et al., 2004), also reflected in spindle characteristics (Z. Y. Zhang et al., 2021) and the anteriorization of slow oscillation onset (Timofeev et al., 2020). Sleep supports learning also during childhood and adolescence (Hoedlmoser, 2020; Kopasz et al., 2010). A TMR study with children aged 11–12 years showed that odor cueing during sleep enhanced learning (Neumann, Oberhauser, & Kornmeier, 2020), suggesting that sleep actively consolidates recent memories within the age group. The influence of developmental state on memory consolidation was scrutinized in a study with an inventive design. In that study, children and adults were tested for object ('what'; intentionally encoded) and context ('where'/'when'; incidentally encoded) memory within the same memory task. Interestingly, only in adults, sleep during the retention decontextualized object memory whereas children tended to preserve the combined episodic representation (Wang, Weber, Zinke, Noack, & Born, 2017). This prompts to examine developmental implications on memory consolidation mechanisms. Contrary to consistent findings on adult (SO-coupled) fast spindles, memory performance in children often associates with spindles from the slow range, and the associations' direction varies and may be confounded by general cognitive abilities (Hahn et al., 2019; Hoedlmoser et al., 2014; Kurdziel, Duclos, & Spencer, 2013). In school-aged children, SO-spindle coupling is relatively weak, i.e. inconsistent (Hahn et al., 2020). While SO-upstate-coupled fast spindles may already predict memory retention within that age group (Kurz et al., 2020), the synchrony strengthens between the ages 10 and 16 (Hahn et al., 2020) along with increased fast spindle density (Hahn et al., 2019). These developmental changes were shown to associate with enhanced memory consolidation (Hahn et al., 2020; Hahn et al., 2019). In the light of these accounts on the oscillatory development, the adolescent sample in this thesis likely exhibited (nearly) adult-like coupling and conformable relevance on learning, predicting memory outcome for items that were intentionally encoded.

Considering the genotypic associations examined within this thesis, there are grounds to presume that age may have confounded the investigation

regarding especially *COMT* Val158Met. As discussed, during the transition from adolescence to adulthood, the influence of $Met_{COMT}$ alleles on prefrontal dopamine levels as well as neural anatomy and connectivity are inverted (Meyer et al., 2016; Raznahan et al., 2011; Wahlstrom et al., 2010). Consequently, the neurophysiological and behavioral findings on Val158Met in this thesis may not be generalizable to adult population. In this regard, the analyses on *BDNF* Val66Met may be less affected. BDNF levels are reported to slowly increse during adolescence (Miguez, Bueno, Espinoza, Chan, & Perez, 2020) and Val66Met has been associated with neurodevelopmental implications (Jasińska et al., 2017). While this may influence neurophysiological metrics such as sleep spindles and oscillatory synchrony in a longitudinal manner, no interaction between Val66Met and age on the activity-dependent BDNF dynamics have been reported, to the best of current knowledge. It is of note that regarding either *BDNF* or *COMT*, the self-reported pubertal status did not differ according to genotype. While measuring pubertal stage does not directly probe neural maturation, the two are considerably intertwined (Herting & Sowell, 2017).

### 6.5.3 THE DEFINITION AND DETECTION OF SLEEP OSCILLATIONS

Sleep spindles and their coupling with SOs were in the core of this thesis (Studies I, III and IV). In sleep research, the methods deployed to identify spindle/SO activity or their coupling are variable. As for the spindle detection algorithm, it was adapted from an approach described by Ferrarelli and colleagues (Ferrarelli et al., 2007). This amplitude-threshold-based algorithm has been criticized especially due to its insensitivity, which results in notably low spindle densities (Warby et al., 2014). In the Studies I, III and IV the method was adjusted by lowering the detection threshold, which resulted in mean spindle densities of ~2.5–5 per minute, depending on the frequency band and location. This converges with a large characterization of sleep spindles within the age group (Purcell et al., 2017).

Spindles in humans are detected rather variably in a range of ~9–16 Hz, the boundary for slow and fast spindles typically settling between ~12 to 14 Hz (Cox, Schapiro, Manoach, & Stickgold, 2017). In this thesis, using either 12 Hz (Study III) or 13 Hz (Studies I and IV) as the lower boundary for fast spindles yielded relatively comparable coupling metrics and memory associations, not only between these studies but also with literature. However, it has been argued that using individualized, instead of fixed, frequency bands for spindle detection is advisable, because identical thresholds do not likely capture optimal power dynamics for all individuals (Cox et al., 2017). Given that the frequency of peak spindle power changes along SO phase (Muehlroth et al., 2019), the chosen spindle range inevitably affects the phase alignment of SO-coupled spindles and likely its behavioral correlates. One study found

individualized spindle range definition, relative to fixed, to better reflect developmental change in memory retention and coupling strength (Hahn et al., 2020). However, it is yet unclear whether an individual power peak invariably denotes the optimal frequency for memory consolidation, or if memory is better served by a less prominent oscillatory activity that coincides with SO peak more precisely. Complementing the issue by further research is undoubtedly in order. Ultimately, the phenomenon, its nature and boundaries are best elucidated when studied with variable approaches.

### 6.5.4 MEMORY TASKS

The implementation of the recognition memory task in Studies I, II and IV requires consideration. Lacking a pre-sleep memory testing precludes deducing that the associations found between sleep oscillations and memory outcome represent mechanistic memory consolidation. Even though such an interpretation is readily drawn, given the accumulated theoretical and experimental basis (e.g. Study III), it remains possible that the relations in these studies indicate a cognitive trait or a pre-sleep process. While the former was partially mitigated by addressing general cognitive ability, learning can intensify NREM oscillations during the following sleep, as discussed in previous chapters. However, this does not render these oscillations irrelevant for memory consolidation. Instead, their wake activity-dependent modulation can ensure that the related synaptic changes, i.e. stored information, are preserved over sleep-related downscaling process.

The recognition memory task was a go/no-go paradigm where only a positive response in case of recognition ('old') was required, instead of a more common old/new-type task. It should be emphasized that it was a deliberate choice to deploy a task with minimal room for misunderstanding in the varying test circumstances (i.e. at the adolescents' homes). The potential caveat in a go/no-go approach is that it does not distinguish between an actual non-recognition and a failure to respond, thus possibly introducing noise in the performance metrics. Go/no-go tasks are rather rarely used in recognition memory studies, in contrast to e.g. lexical decision tasks where the approach may actually provide faster and more accurate responses compared to two-choice option (Perea, Rosa, & Gómez, 2002). It has been argued that even though a lack of response may in some occasions result from e.g. distraction, go/no-go as a memory task suits for recognition memory (Boldini, Russo, & Avons, 2004). In fact, one study found that two-choice and go/no-go tasks yielded close-to-identical 'old' responses in a recognition memory task (Gomez, Ratcliff, & Perea, 2007). When calculating recognition accuracy (*d'*), only 'old' responses are needed.

# 7 CONCLUSIONS

Sleep is elemental for enduring memories. The milieu that is devoid of sensory inflow prevents recent bits of encoded information from being overwritten. At the same time, recurrent sleep oscillations replay certain memories, strengthening and re-distributing their neural representations enabling later retrieval. This thesis investigated how sleep and specific neural oscillations associated with memory performance. Better memory outcome was related to especially fast sleep spindles and their precise synchrony with slow oscillations. This aligns with the conception that fast spindle-coincided depolarization provides a specific neuronal state for plasticity. Indeed, similar associations were not observed regarding the synchrony between slow oscillations and slow spindles, or between temporally overlapping fast sleep spindles.

A major question in this thesis was whether certain gene polymorphisms previously attributed to neuroplasticity affected sleep oscillations and their contribution to memory performance. Primarily, it was found that *BDNF* Val66Met moderated the associations how sleep spindles and their SO-coupling predicted overnight memory outcome, while the oscillatory properties as such were not affected. Within the boundaries of this thesis the exact underpinnings of the phenomenon are not discernible. Speculatively, increased propensity for synaptic plasticity in the carriers of two $Val_{BDNF}$ alleles may elevate the strength with which the recurrent oscillatory events imprint and re-distribute labile memory traces.

The understanding on the potential and constraints of sleep's benefit on learning is accumulated by considering inter-individual variability in neurophysiological correlates of memory processing. The approach has thus far been largely unadopted. As shown in this thesis, the relation between sleep and memory may depend on inherited factors, questioning whether the benefits of sleep on memory are constant and equal across individuals.

## 7.1 FUTURE DIRECTIONS

This thesis provoked questions to which only further studies can answer. First, the extent to which sleep (oscillations) associate with overnight memory seems not substantially affected by certain methodological elements like the participants' age (between adolescence and early adulthood) and memory task type. However, whether this also applies to the genotypic moderation observed in this thesis in unclear, and studies deploying variable tasks and sample constitution are warranted. Especially, a longitudinal examination within the

Glaku cohort would provide fascinating data on the development and significance of sleep oscillations between adolescence and adulthood. Another interesting approach to probe the possible genotypic influence on sleep oscillations and memory is targeted memory reactivation. Are individuals equally receptive for experimentally manipulated reactivations of novel memory traces? Along the same vein, tying (targeted) memory reactivations with suboptimal SO phase may work as a mechanism for forgetting, opening intriguing possibilities in different fields, e.g. mental health. Finally, the exact contribution of sleep on emotional memory keeps puzzling researchers. Some evidence suggests that the unfolding of the issue requires addressing situational stress. Thus, extending investigation to the state and events of autonomous nervous system could clarify the issue beyond neural oscillations.

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