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Recent advances in memory consolidation and information processing during sleep

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Abstract

Increasingly studied in a systematic manner since the 70', the cognitive processes of the brain taking place during sleeping periods remain an important object of scrutiny in the scientific community nowadays. In particular, sleep has been demonstrated to play a significant role for learning and memory consolidation processes, and sleep scientists have started unravelling its underlying neurophysiological mechanisms. However, sleep remains a multidimensional phenomenon, and many questions are left open for future research. In this selective review article, we address recent advances in particular domains in which sleep research further progressed in the past decade. We highlight the developmental trajectory of sleep-dependent learning and memory consolidation processes, from their development in childhood to their potential impairments in ageing, and the nature and extent of our capabilities for information processing, learning and memory reinforcement capabilities during sleep.

Keywords: learning, development, ageing, hypnopaedia

Introduction

The relationships between sleep and memory became a topical issue over the past decades. From a tentative hypothesis pushed forward by a few animal and human precursors in the 70's (e.g., Fowler, Sullivan, & Ekstrand, 1973; Koukkou & Lehmann, 1968; Smith, Kitahama, Valatx, & Jouvet, 1974; Tilley & Empson, 1978), it is nowadays well established that sleep plays a significant role in learning and memory processes, complementary to those taking place during wakefulness. In particular, many studies conducted in the 90's and the following decades evidenced a role for post-training sleep in the consolidation of newly learned material in humans, further supported by neuroimaging data evidencing continued learning-related brain activity during sleep. Studies also revealed that sleep deprivation impacts activity in brain networks necessary for optimal cognitive function and learning (for reviews see e.g. Chee & Chuah, 2008; Peigneux, 2015; Peigneux, Laureys, Delbeuck, & Maquet, 2001; Rasch & Born, 2013). In this short review, we will focus on recent advances in a subset of domains in which sleep research further progressed significantly in the past decade, i.e., learning and memory consolidation in relation to sleep in a developmental perspective (from childhood to ageing), and information processing and memory reinforcement capabilities during sleep. This should not obscure the fact that, besides the subdomains reviewed here, the beneficial effects of sleep and its functions are manifold (Bodizs, 2021). In particular, sleep is intimately linked to the efficiency of many cognitive and emotional functions (Simor, Sifuentes-Ortega, & Peigneux, 2021), that certainly deserve great interest but are beyond the scope of the present review.

Sleep and memory in children

Especially infants, toddlers and children accumulate high amounts of memories during the day. At the beginning, these memories are fragile and susceptible to interference or decay, especially when sleep is qualitatively and/or quantitatively inadequate. A meta-analysis (Astill, Van der Heijden, Van Ijzendoorn, & Van Someren, 2012) showed that insufficient sleep in children (5-12 years) is associated with deficits in high-order and complex cognitive functions like memory, and an increase

in behavioural problems. In a longitudinal study (Seegers et al., 2016), 1192 parents reported their children's nocturnal sleep duration annually from age 2.5 to 10 years. It was found that short persistent sleep duration is associated with poor vocabulary performance in middle childhood. Since 1955 when Aserinsky and Kleitman (1955) first assessed eye movements and their potential relationship with sleep depth in infants, there has been a constant growth in sleep research in children investigating not only sleep duration but also sleep quality and sleep physiology. Nowadays, there is consensus that sleep enhances memory consolidation for various memory domains in children, especially regarding declarative (explicit) memory (Ashworth, Hill, Karmiloff-Smith, & Dimitriou, 2014; Hahn et al., 2019; Hahn, Heib, Schabus, Hoedlmoser, & Helfrich, 2020; Peiffer, Bricet, De Tieghe, Peigneux, & Urbain, 2020; Wang, Weber, Zinke, Inostroza, & Born, 2018; Wilhelm, Diekelmann, & Born, 2008). A study examining implicit and explicit knowledge for motor sequence learning (Wilhelm et al., 2013) showed that children demonstrate even greater gains in sleep-dependent explicit knowledge than adults. Consistent with findings in adults, memory consolidation in children seems to be mainly influenced by NREM and slow wave sleep (SWS) for declarative, but not always procedural (motor, implicit) memories (Backhaus, Hoeckesfeld, Born, Hohagen, & Junghanns, 2008; Henderson, Weighall, Brown, & Gareth Gaskell, 2012; Wilhelm et al., 2008; Wilhelm, Prehn-Kristensen, & Born, 2012). Some studies suggested that procedural memory is not dependent on sleep to the same extent in children than in adults (Fischer, Wilhelm, & Born, 2007; Wilhelm et al., 2012), but performance gains may also be sensitive to the different levels of memory performance before sleep. Furthermore, word acquisition and consolidation were shown modulated by both nocturnal and daytime sleep (Henderson et al., 2012; Tham, Lindsay, & Gaskell, 2015; Williams & Horst, 2014). The findings of a larger sleep benefit in children compared to adults for lexical integration was further replicated (James, Gaskell, & Henderson, 2019). Last but not least, sleep was also found to be beneficial for emotional memory. For instance, sleep prevents the forgetting of reward-associated memory representations, an effect even more pronounced in children than in adults (Prehn-Kristensen et al., 2009).

Three main theories currently dominate the current literature about sleep and memory consolidation: (1) the active systems consolidation theory suggests a replay of new memories involving a dialogue between the hippocampus and cortex representing a window of potential cortical plasticity (Buzsaki, 1998; Diekelmann & Born, 2010). This dialogue is supported by slow oscillations (SO; < 1Hz), sleep spindles (~12-16 Hz) as well as sharp-wave ripple activity; thereby, new memories are strengthened and subsequently integrated into long-term memory (Figure 1A and 1B); (2) the synaptic homeostasis hypothesis (SHY; Tononi & Cirelli, 2006, 2014) is a model proposing that SWS encourages synaptic downscaling, or the elimination of weak neural connections, leading to the retention of only the strongest memories. Following this theory, SWS is not only beneficial for neuronal communication but also memory management; (3) finally, the contextual binding theory (Yonelinas, Ranganath, Ekstrom, & Wiltgen, 2019) proposes that sleep does not involve an active process, but only serves to reduce interference by providing a contextual shift that preserves the original memory trace.

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FIGURE 1

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Recently, there is growing evidence especially in favour of the active systems consolidation theory. Several studies suggest that a precise temporal coordination between SOs and sleep spindles is a key mediator for sleep-associated memory consolidation across the lifespan (Hahn et al., 2020; Helfrich, Mander, Jagust, Knight, & Walker, 2018; Joechner, Wehmeier, & Werkle-Bergner, 2021; Mikutta et al., 2019; Molle, Bergmann, Marshall, & Born, 2011; Muehlroth et al., 2019). SOs and sleep spindles are well known to be related to the neural integrity of memory structures such as medial prefrontal cortex, thalamus, hippocampus, and entorhinal cortex (Helfrich, Lendner, & Knight, 2021; Helfrich et al., 2018; Ladenbauer et al., 2017; Mander, Winer, & Walker, 2017; Muehlroth et al., 2019; Spano et al., 2020; Winer et al., 2019). Furthermore, SOs are traveling waves and thus a marker for brain connectivity. Schoch et al. (2018) investigated using high-density EEG across-night

dynamics of traveling SOs during sleep in children from preschool-age (2–5 years) to young adolescence (9–17 years). They demonstrated that brain connectivity undergoes across-night dynamics specific to maturational periods. SO propagation distance decreased across a night of sleep, which was dependent on age and most prevalent in preschool children. The authors propose that these changes represent important milestones in maturational brain processes and that slow waves are therefore important markers for neurodevelopment, directly involved in human brain development processes (for a review see Timofeev et al., 2020). Focusing on SO - sleep spindle coupling (Figure 1C and 1D), it is suggested that these orchestrated sleep oscillations not only actively transfer newly encoded memories during sleep but also indicate general efficiency of memory pathways (Helfrich et al., 2021; Mander, Winer, et al., 2017). Hahn and colleagues (2020) found that SO – sleep spindle coordination became not only more consistent from childhood to late adolescence but also directly predict enhancements in declarative memory formation across development. Regarding complex real-life motor learning, there is only rare knowledge about the impact of sleep. However, overnight performance benefits for riding an inverse steering bike have been shown to be related to spindle activity in adolescents and adults (Bothe et al., 2019, 2020). Similarly, juggling performance increased after sleep and juggling training induced power increments in the spindle and SO frequency range during a nap (Morita, Ogawa, & Uchida, 2012, 2016). Hahn et al. (2022) investigated the role of the orchestration between SOs and sleep spindles for procedural (motor) learning utilizing a juggling-training across age groups. The results provided evidence that regionally specific, precisely coupled SOs and sleep spindles also support gross-motor learning.

Not only nocturnal but also diurnal sleep is known to support memory formation. Especially during the early years of life, naps need to be taken into consideration and seem to have a unique role for the early cognitive development. Children’s diurnal sleep is mainly made up of SWS and is known to enhance episodic (Lahl, Wispel, Willigens, & Pietrowsky, 2008), visuospatial (Lokhandwala & Spencer, 2021) and declarative memory (Horvath, Myers, Foster, & Plunkett, 2015; Kurdziel, Duclos, & Spencer, 2013). Especially sleep spindles during diurnal sleep have been shown to benefit

visuospatial learning already during early childhood (Kurdziel et al., 2013). Using a novel storybook task, Lokhandwala and Spencer (2021) found that performance in children aged 36-71 months was better following a nap compared to an equivalent interval spent awake. Moreover, performance remained better the following day if a nap followed learning. Time spent in SWS during the nap was positively associated with the increase in performance. Taken in conjunction with their prior work (Kurdziel et al., 2013), these results suggest that not only SO and SWS but also sleep spindles during naps may contribute to declarative memory processing already during early childhood. Likewise, a magnetencephalography study recorded brain activity of school-aged children (8.0–12.5 years) to explore the specific impact of diurnal sleep (90 min nap) on the neurophysiological processes during learning and consolidation of declarative memories (i.e., novel associations between unknown objects and their functions). Learning-dependent changes were observed within hippocampal and parahippocampal regions, followed by sleep-dependent changes in the prefrontal cortex, whereas no equivalent changes were observed after a similar period of wakefulness (Urbain et al., 2016). Further, they found that learning-related activity in (para)hippocampal regions was correlated with increased SWS activity during the post-training nap, which was specific to the newly learned representations.

In conclusion for this section, we emphasize here new insights about investigating sleep and memory in infants, toddlers and children. Although the finding that sleep in comparison to wakefulness benefits the consolidation of memories is well established, the underlying theoretical frameworks trying to explain the benefits of sleep for memory still strive for more substantiated findings, including biological and physiological correlates, and especially in a developmental perspective. This applies also to the upcoming ageing section, wrapping up recent advances in the field of sleep and memory at the other end of the age spectrum.

Sleep and memory in ageing

Age-related changes in sleep quality and their impact on memory consolidation and brain health have received increasing attention in the recent years. In the following, we will synthesize the main results on the coupling between slow waves and spindles in ageing, and its impact on memory consolidation. We will also report on neuroimaging studies exploring the underpinnings of these impairments. Finally, prospective memory, or the memory for the intentions to perform in the future, has been a novel focus lately.

Altered temporal coupling between slow oscillations and sleep spindles in ageing

As mentioned above, sleep-dependent memory consolidation is a complex process involving neuronal reactivations, slow oscillations, sleep spindles, etc, that may all be altered with increasing age. The precise temporal coupling of slow oscillations and sleep spindles, which appears to be crucial for an efficient consolidation of memory traces, seems altered in older adults and may compromise overnight memory consolidation (Helfrich et al., 2018; Muehlroth et al., 2019). Abnormal coupling in older adults has been associated with greater medial prefrontal cortex atrophy (Helfrich et al., 2018). These results on temporal coupling of slow-wave and spindles are particularly interesting, as they can represent novel target for clinical interventions (Ladenbauer et al., 2017). In addition, altered coupling between slow waves and spindles has also been shown to correlate with tau aggregation amongst cognitively intact older adults, suggesting that this coupling could be a potential biomarker for the pathogenesis of early Alzheimer's disease (Winer et al., 2019).

There is nowadays an increasing interest in investigating the associations between brain integrity and sleep-dependent memory consolidation in older adults. In a group of older adults, atrophy of the medial prefrontal cortex was associated with reduced slow wave activity, which in turn was associated with worsened overnight retention of word pairs (Mander et al., 2013). Likewise, similar associations between frontal SWA and both overnight change in spatial navigation performance and medial prefrontal cortex volume were reported in young and old adults (Varga et al., 2016). In addition in old adults, the structural integrity of brain areas generating slow oscillations

and sleep spindles, including the medial prefrontal cortex, the hippocampus, the entorhinal cortex and the thalamus is associated with a better slow oscillation-spindle coupling (Muehlroth et al., 2019). Another study showed that β -amyloid aggregates within the medial prefrontal cortex are associated with reduced SWS, this again impairing memory consolidation (Mander et al., 2015). Overall, these data suggest that age-related brain alterations may eventually lead to changes in slow oscillations and sleep spindles, and also in their fine-tuned coupling, which will ultimately impair memory consolidation. However, one study provided results that challenged the view according to which impaired sleep-dependent memory consolidation in elders is due to changes in SWS or more broadly in NREM sleep. Indeed, Frase et al. (2020) reported that participants with smaller hippocampal, parahippocampal and medial prefrontal cortex volumes exhibited a reduced overnight declarative but not procedural memory consolidation. In addition, mediation analyses revealed an effect of age on sleep-dependent declarative memory consolidation, but no significant mediation effects of brain structural parameters (i.e., hippocampal, parahippocampal and medial prefrontal cortex volumes) on this association. Moreover, the effects of age and brain integrity on overnight declarative memory consolidation were not mediated by sleep variables (i.e., spectral power in the different EEG frequency bands). In other words, this study suggests that impaired sleep-dependent memory consolidation in old adults does not necessarily depend on slow-wave sleep as previously reported, or at least not solely. Further investigations are needed to better understand these conflicting results, exploring for instance factors such as the individual's cognitive reserve that might help to tolerate age-related changes in sleep and maintain good memory performance, and using more fine-grained investigations of brain structural alterations.

As for motor memory, sleep-dependent consolidation of motor tasks was found generally impaired in older adults (King, Fogel, Albouy, & Doyon, 2013), an impairment associated with a reduction in sleep quality (Fogel et al., 2014; Mander, Zhu, et al., 2017) and reduced striatal activity (Fogel et al., 2014). In addition, greater cortico-striatal activation during initial learning of a motor sequence learning task has been associated with better consolidation in old adults, but only when

they are given the opportunity to nap between the training and retest sessions (King et al., 2017). In a study with successive resting state fMRI scans administered before and after motor sequence learning training, and after a retention interval consisting of a nap or an equivalent period of wakefulness, old adults exhibited a completely different pattern of functional connectivity changes in cortico-striatal regions during motor sequence learning consolidation as compared to young individuals. Furthermore, in old participants, functional connectivity changes were not associated with performance gains as reported in young ones (Fang et al., 2021). Finally, several studies investigated whether changes in white matter integrity might explain the reduced benefit of sleep to motor skills memory consolidation in ageing. Since the degree of degeneration of white matter tracts connecting cortical sensorimotor control areas or thalamo-cortical areas determines the propagation of sleep spindles and their related memory benefits (Mander, Zhu, et al., 2017; Vien et al., 2019), white matter integrity might be a key mechanism modulating the expression of sleep-dependent offline gains following motor sequence learning in young and old adults.

Prospective memory

Another domain that developed in the recent years is prospective memory, evaluating whether sleep can also reinforce our memories for intentions to perform in the future. Prospective Memory (PM) refers to the ability to remember to execute an intention at the appropriate moment in the future. Sleep-dependent consolidation of intentions has been assessed in young adults, leading to mixed results. Meta-analytical results indicate that the benefit of sleep on PM is statistically significant but in the small to medium range (Leong, Cheng, Chee, & Lo, 2019). In old adults, results are also controversial. In a first study, participants performed a semantic categorization task and then encoded intentions comprising related and unrelated cue-action pairs. They were instructed to remember to perform these actions in response to cue words presented during a second semantic categorization task administered 12 hours later, after a retention interval filled with either daytime wakefulness or nocturnal sleep. For related intentions, sleep compared to wakefulness benefited

performance in young but not in old adults. There was no benefit of sleep for unrelated intentions, whatever the age group. Finally, the proportion of time spent in SWS was positively associated with performance for related intentions in young adults only (Leong, Lo, & Chee, 2021). According to the authors, these results indicate that sleep-dependent consolidation of intentions is impaired in ageing and that the link between sleep and memory is functionally weakened in old adults. Using an original task consisting in a walk in a virtual environment, Rehel et al. (2019) assessed the consolidation of various types of intentions (i.e., time-based intentions that need to be performed after a certain amount of time, or event-based intentions to be implemented at the appearance of a cue in the environment), also varying the strength of the link between the intention and the cue, after a daytime or night-time retention interval in young and old adults. They showed that PM was not affected by age, whatever the type of intentions and the nature of the retention interval (sleep/wake), indicating that when assessed using complex realistic situations, PM is not impaired in ageing. Sleep reinforced all types of intentions in young adults. In older adults, all intentions benefited from sleep, except for event-based ones with a weak link between the cue and the action to perform. Finally, Scullin et al. (2019), using a laboratory paradigm, showed PM impaired in old adults. PM performance was not associated with frontal delta power, slow oscillations, or spindle density, but with REM sleep duration. To sum up, these results highlight the complexity of the links between sleep and memory, and the difficulty of comparing studies that used different cognitive paradigms. Finally, the suggestive evidence for links between PM and REM sleep raises the question of the existence of potential compensatory mechanisms for reduced consolidation processes during sleep with increasing age (Scullin & Gao, 2018). Further studies are needed to understand how REM and NREM sleep may interact to promote efficient cognitive functioning and memory consolidation processes in old adults.

Recent advances in information processing, learning and memory during sleep

Can we learn during sleep?

Hypnopaedia, i.e., the learning of novel information by being exposed to it during sleep (Figure 2, bottom row), has been a popular hypothesis in the 50's, to the point that it was used as a marketing argument to boost the sale of individual tape recorders. Actually, the concept was popularised 20 years earlier by the writer Aldous Huxley in its famous dystopia "Brave New World" (1932), in which hypnopaedia is used in dormitories for the purpose of mass manipulation and indoctrination during sleep. Notwithstanding, subsequent systematic and sleep-controlled studies invalidated the hypothesis by evidencing methodological caveats (e.g., the elements recalled the next day were associated with documented EEG arousals during exposure in the sleep period, suggesting that learning took place in an intermediate awake state; (Emmons & Simon, 1956; Tani & Yoshii, 1970) or disclosing null results (e.g., no learning for verbal material; (Wood, Bootzin, Kihlstrom, & Schacter, 1992). It was thus considered for a long time that in-sleep learning of *de novo* information is not a viable option, even if the human brain is able to continue processing and monitor external information during sleep (e.g., Blume, Del Giudice, Wislowska, Heib, & Schabus, 2018), although with markedly attenuated sensitivity to high-order cognitive processes (e.g., disrupted predictive coding or detection of simple arithmetic violations; Strauss & Dehaene, 2019; Strauss et al., 2015). Still, the hypnopaedia hypothesis was revived in the last decade with a seminal study showing that conditioning auditory tones to respiratory responses associated with pleasant or unpleasant odours can be achieved both in REM and NREM sleep, and that in-sleep conditioning in NREM sleep transfers to subsequent wakefulness (Arzi et al., 2012). The same authors further showed that olfactory aversive conditioning during sleep helps reducing the rate of cigarette smoking (Arzi et al., 2014). This logically led to question the type of information/association that can be learned during sleep, and in which state of sleep. Repeated exposure to novel noise patterns during REM or light NREM sleep was found to improve behavioural performance upon awakening, whereas it was deteriorated after exposure during deep NREM sleep (Andrillon, Pressnitzer, Leger, & Kouider, 2017). Although the authors hypothesized facilitative and suppressive plasticity mechanisms respectively

taking place in REM/light NREM and deep NREM sleep, the results are in opposition with Arzi et al. (2012) who found the opposite pattern of transfer of learned associations at wake after conditioning in NREM but not in REM sleep. Other studies investigated more sophisticated forms of learning than conditioning or perceptual learning. Auditory magnetoencephalographic (MEG) frequency-tagged responses mirroring ongoing statistical learning were evidenced during wakefulness but not NREM sleep, suggesting that statistical regularities remain undetected during NREM sleep (Farthouat, Atas, Wens, De Tiege, & Peigneux, 2018). Similarly, Makov et al. (2017) found intact EEG responses to auditory sound streams both during NREM and REM sleep, but no identifiable signs of hierarchical parsing of the continuous stream of syllables into higher-order elements such as words, phrases, and sentences. In the musical domain, EEG frequency-tagged responses provide a neural representation of rhythm processing and reflect the emergence of high-order representations such as the pulse-like meter perceived while listening to music. As compared to wakefulness, EEG recordings during the presentation of regular and irregular rhythms disclosed preserved processing of low-level acoustic properties but a selective attenuation of frequency-tagged responses at meter-related frequencies during REM sleep, and a complete suppression in NREM sleep (Sifuentes-Ortega, Lenc, Nozaradan, & Peigneux, 2021), suggesting limited higher-order processing of auditory rhythms during sleep. Altogether, these studies suggest intrinsic limitations in in-sleep learning that might restrict the sleeping brain's learning capabilities to simple, elementary associations. In another study however, participants were exposed during NREM sleep to word pairs composed of a pseudoword and a concrete word depicting either a large (e.g., house) or small (e.g., shoes) object, and then tested the next day in a forced choice test asking whether the associated pseudoword would fit in a box, i.e., being implicitly associated with the large or small feature of the paired concrete object. Results showed that when the presentation of the second word of a pair in NREM sleep coincided with an ongoing slow-wave peak, the chances increased for responses compatible with the associated object in the next day's forced choice test, i.e., suggesting implicit vocabulary learning (Zust, Ruch, Wiest, & Henke, 2019). A re-analysis of Zust et al. (2019) data found that sleep-learning diminished

subsequent awake-learning when participants learned semantic associations that were congruent to sleep-learned associations, but not when they learned associations that conflicted with it (Ruch, Alain Züst, & Henke, 2022). Although Züst et al. (2019) interpreted their results as demonstrating the occurrence of implicit relational binding during peaks of slow oscillations, an alternative explanation would be that perceptual, i.e., lower-level, pseudoword-word associations have been created during sleep, and then higher-order relational binding took later place only at wake when being presented with the pseudoword evoked the associated word, thus driving the decision in the forced-choice test. Future studies are still needed to delineate the mechanisms subtending, and the extent of, the human brain's spontaneous learning capabilities during sleep.

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FIGURE 2

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Can we modulate previously learned information during sleep? The cases of targeted memory reactivation (TMR) and ongoing sleep stimulation

Animal (e.g., Ji & Wilson, 2007; Margoliash, 2010) and human (e.g., Maquet et al., 2000; Peigneux et al., 2004; Peigneux et al., 2003; Schonauer et al., 2017) studies have evidenced the spontaneous replay of neural activity patterns associated with awake experience and learning during post-training episodes of REM and NREM sleep (for a comprehensive review, see e.g., Rasch & Born, 2013; Figure 2, top row) These observations are in line with the neural replay hypothesis proposing that memories are consolidated through the spontaneous reactivation of learning-related neural patterns (Skaggs & McNaughton, 1996) and the hippocampo-neocortical transfer of the associated information during sleep stages (Buzsaki, 1998). The past decade has witnessed the development of a new paradigm expanding on this assumption by showing that presenting during post-learning sleep specific cues previously associated with elements of the learning episode actually leads to improved memory

performance (Figure 2, middle row). For instance, re-exposure during SWS to an odour previously associated with an object-location declarative memory task was shown to trigger hippocampal activity in sleep, and improve overnight performance as compared to a normal sleep condition (Rasch, Buchel, Gais, & Born, 2007). This procedure, known as sleep targeted memory reactivation (TMR), works under the assumption that presenting learning-related cues during sleep will trigger the neurophysiological mechanisms subtending neural replay (see for reviews Hu, Cheng, Chiu, & Paller, 2020; Oudiette & Paller, 2013), thus reinforcing spontaneous memory-related consolidation activity and brain plasticity. This assumption must be taken cautiously however, as it was shown that maintaining artificially high the cholinergic tone during SWS by administering physostigmine does not impair memory consolidation performance in an odour cueing TMR protocol (Klinzing et al., 2018), whereas it is known to do so in spontaneous, untriggered post-training SWS (Gais & Born, 2004). It suggests that triggered (i.e., odour cued) and spontaneous memory reactivation are not merely superposable and do not entirely rely on the same neuropharmacological mechanisms. Nonetheless, TMR during sleep is a popular paradigm and has now been used in a wide number of studies, that it is not possible comprehensively reviewing here. A meta-analysis conducted over 91 experiments concluded on a positive effect on performance of sleep TMR during NREM sleep stages N2 and slow-wave sleep, but not during REM sleep or wakefulness, across multiple domains including declarative and procedural memory (Hu et al., 2020). Available evidence indeed supports the notion that NREM sleep oscillatory activities may be the key neurophysiological mechanisms underlying a positive role of TMR in the consolidation of recent memories. For instance, auditory cueing of learned verbal or musical material during NREM sleep increases spindle-related activity and improves recall (Farthouat, Gilson, & Peigneux, 2017; Schreiner, Lehmann, & Rasch, 2015) and motor execution (Antony, Gobel, O'Hare, Reber, & Paller, 2012) on the next day, and disruption of sleep spindles due to external stimulation after cueing annihilates the otherwise observed overnight performance gains (Farthouat et al., 2017; Schreiner et al., 2015). Using graph theory analysis, another study found that reactivating object-location memories with associated auditory cues during

SWS increases occipital activity integration with a memory-replay related brain network, correlated with overnight memory stabilization (Berkers et al., 2018). Also, administration of GABA agonist zolpidem coupled with TMR during SWS resulted both in enhanced memory performance and increased coupling of fast spindles and theta to slow oscillations (Carbone et al., 2021). Likewise, local TMR (i.e., unilateral odour cueing in sleep after lateralized learning) improved phase-amplitude coupling (PAC) between slow oscillations and sleep spindles in the cued hemisphere, suggesting that TMR in human sleep selectively promotes specific memories associated with local sleep oscillations (Bar et al., 2020). As mentioned above, evidence for an effect of TMR during REM sleep is less consistent and did not emerge from meta-analytic reviews (Hu et al., 2020). Still, this does not detract from the possibility that REM sleep plays at the very least a complementary role in the processing of cued memories during sleep. For instance, the time spent in REM sleep after cueing during NREM was shown to predict the amplitude of memory consolidation effects (Tamminen, Lambon Ralph, & Lewis, 2017). It suggests that information cued in NREM sleep continues being processed in the physiologically ensuing REM stage, in line with the sequential hypothesis of the function of sleep postulating that the elaboration of memory traces acquired at wake requires two sequential steps taking place during SWS then REM sleep (Giuditta et al., 1995). Accordingly, a study conducted in patients with narcolepsy who often fall asleep directly in REM sleep found that NREM sleep spindles are associated with memory consolidation performance in a nap, but only when NREM is followed by REM sleep (as opposed to a REM-NREM sequence), that is in a physiologically ordered succession of sleep stages (Strauss et al., 2022). Also supporting a complementary role of REM and NREM sleep, TMR differentially impacted temporal delays in dream reactivation following the learning of a virtual reality flying task as a function of the stimulated sleep stage: task-related dreams were incorporated 1-2 days later after REM sleep TMR, and 5-6 days later after SWS sleep TMR, as compared to no cueing (Picard-Deland & Nielsen, 2022). Finally, it is worth noticing that if NREM sleep oscillations and phasic events (e.g., spindles) are well studied and delineated in relation to memory and TMR, the heterogeneous nature of REM sleep with its phasic and tonic constituents

(Simor, van der Wijk, Nobili, & Peigneux, 2020) has been largely neglected so far, which may obscure potential contributions to the processing of cued memories.

Finally, an even more recently emerging paradigm is the ongoing stimulation of sleep oscillations by external sensory stimulations. Although several studies consistently showed that it is possible entraining and boosting NREM slow oscillations and/or spindles using rhythmic or closed loop acoustic, tactile or electrical stimulations (e.g., Henin et al., 2019; Navarrete et al., 2020; Pereira et al., 2017; Ruch et al., 2021; Simor et al., 2018), it is less clear how and to what extent boosting slow oscillations or spindles during post-training sleep benefits memory consolidation, and several studies concluded to null effects (e.g., Henin et al., 2019; Pereira et al., 2017; Ruch et al., 2021). Still, a meta-analysis conducted over 11 experiments found that acoustic enhancement of SWS indeed tends to increase the overnight consolidation of episodic memory, but with only small and at trend level effects (Wunderlin et al., 2021). Hence, there seems to be nowadays insufficient evidence to support the unreserved use of such approaches to improve memory consolidation processes in human, and even more in pathological conditions associated with memory alterations, even if it represents a promising avenue to understand the underlying neurophysiological mechanisms and develop in the future better adapted individualized interventions to improve sleep and memory.

Concluding remarks

As reviewed in this paper, research on sleep and memory consolidation is still an extremely dynamic field with many exciting avenues to explore. Recent studies have attempted to unravel sleep-dependent memory consolidation process in great details, how it operates, develops and might be disrupted throughout the lifespan. Structural, functional and molecular neuroimaging studies now allow to go further in the understanding of the brain substrates of sleep-dependent memory consolidation and its evolution throughout childhood as well as its impairment during ageing. Finally, new learning during sleep, the sleeping brain's processing capacities and the way we can modulate previously learned information during sleep still continue to raise fascinating questions that

challenge the creativity of a new generation of sleep scientists to develop original and clever neurocognitive paradigms. As the field is growing, many questions still remain to answer, amongst these the specific and complementary contributions of NREM and REM sleep stages, the extent and limits of processing capabilities in sleep, and how sleep's role(s) and functions evolve across the lifespan. In this respect, sleep research remains a worth and gratifying scientific journey, still as exciting as it was for the pioneers in the field. To paraphrase the great French precursor and sleep neurobiologist Michel Jouvet (1925-2017), happy those who enter the field of sleep as so much remains to be discovered and understood!

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FIGURE LEGENDS

Figure 1. Active systems consolidation theory. (A) (1) New information is simultaneously encoded in the neocortical networks (blue) and hippocampus (red). Through repeated hippocampal replay (red lines), memory traces are integrated into existing cortical networks and consolidated. (2) Consolidated memory traces (thick red lines) are resistant to interference and increasingly independent from hippocampal activation. (B) Temporal hierarchy of sleep oscillations mediating the hippocampal-neocortical dialogue: neocortical SO (blue) facilitate thalamo-cortical sleep spindle activity in their depolarizing phase. Sleep spindles (pink) nest hippocampal sharp-wave ripples (red) in their troughs. Through this precisely timed interplay, freshly encoded memories are replayed, potentiated, transformed, and eventually embedded in the neocortex for long-term storage. (C) Representation of SO-spindle coupling in the time domain. The spindle oscillation (pink) follows and underlying SO-component (blue). Note that spindle peak and SO peak coincide. (D) Representation of SO-spindle coupling in the time frequency domain. Power in the spindle frequency band (~11 – 15 Hz) is modulated as a function of SO-phase. Spindle power is diminished in the hyperpolarizing SO-trough at 0 s, but enhanced in the depolarizing SO-peak (dashed line). (Reproduced from M. Hahn 2021, Doctoral dissertation, page 33)

Figure 2. Main sleep-related paradigms for memory consolidation and learning in sleep. [Top row] In the **Spontaneous Reactivation (SR)** condition, participant learn new material during wakefulness; information is then reactivated (neural replay) and consolidated during sleep, eventually leading to stabilized/enhanced performance at retrieval the next day. [Middle row] In the **Targeted Memory Reactivation (TMR)** condition, participants learn new material during wakefulness in a specific context (e.g., sounds); this context presented again during sleep selectively triggers the reactivation process, further reinforcing sleep-dependent memory consolidation effects and improving performance on the next day for the cued (triggered) material. [Bottom row] In the **Hypnopaedia (HP)** condition, a new learning material is presented during sleep, and novel associations are created;

these associations can then be retrieved during subsequent wakefulness, demonstrating in-sleep learning capabilities.

Figure 1.

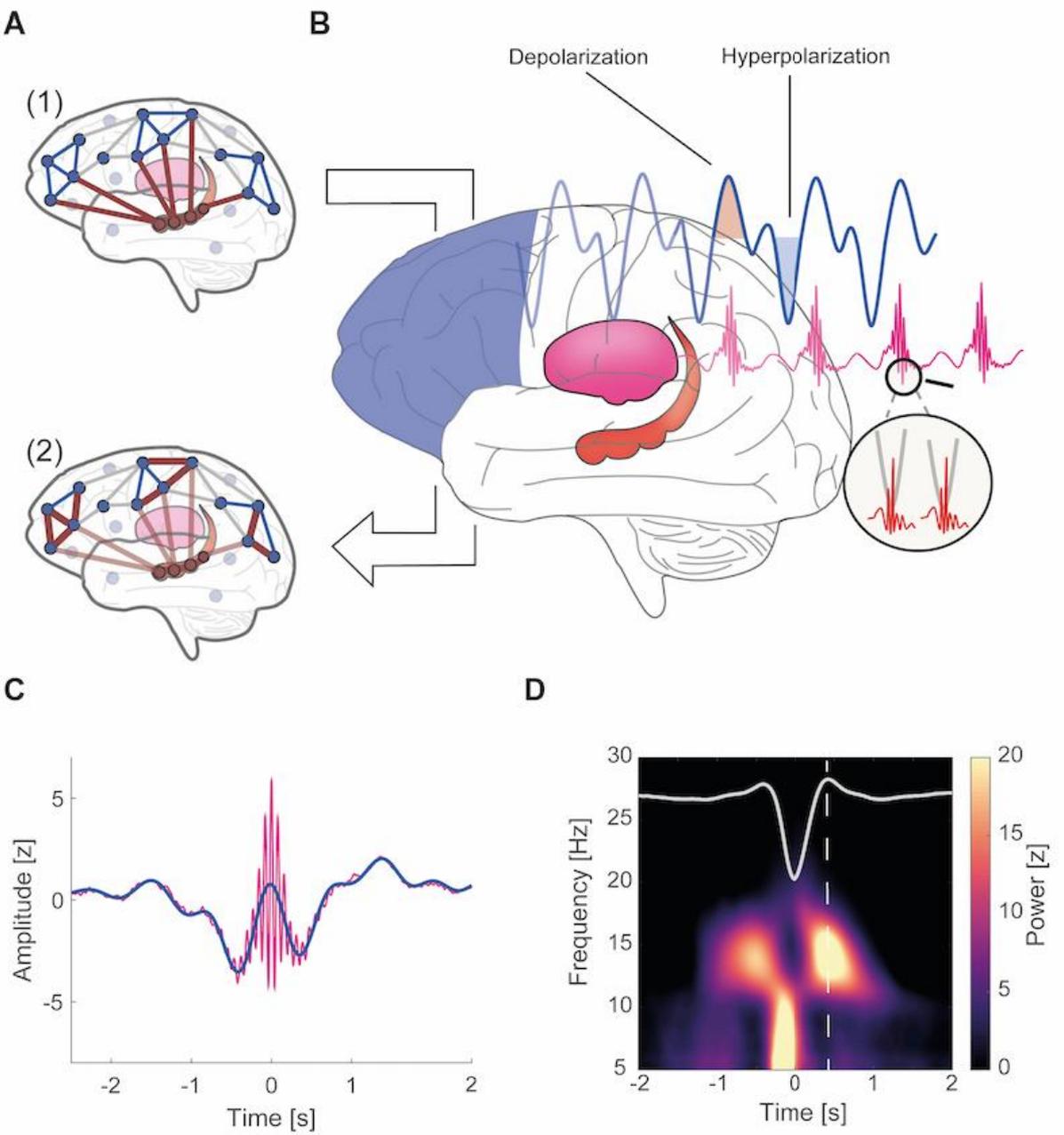


Figure 2.

