Review

Sleep-dependent memory consolidation – What can be learnt from children?

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ABSTRACT

Extensive research has been accumulated demonstrating that sleep is essential for processes of memory consolidation in adults. In children and infants, a great capacity to learn and to memorize coincides with longer and more intense sleep. Here, we review the available data on the influence of sleep on memory consolidation in healthy children and infants, as well as in children with attention-deficit/hyperactivity disorder (ADHD) as a model of prefrontal impairment, and consider possible mechanisms underlying age-dependent differences. Findings indicate a major role of slow wave sleep (SWS) for processes of memory consolidation during early development. Importantly, longer and deeper SWS during childhood appears to produce a distinctly superior strengthening of hippocampus-dependent declarative memories, but concurrently prevents an immediate benefit from sleep for procedural memories, as typically observed in adults. Studies of ADHD children point toward an essential contribution of prefrontal cortex to the preferential consolidation of declarative memory during SWS. Developmental studies of sleep represent a particularly promising approach for characterizing the supra-ordinate control of memory consolidation during sleep by prefrontal-hippocampal circuitry underlying the encoding of declarative memory.

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1. Introduction

From the cradle to the grave we accumulate great amounts of memories that enable us to effectively cope with environmental challenges and also define who we are. The developing brain with its particularly high capacity for plasticity easily acquires basic motor skills like running, speaking and writing as well as fundamental knowledge about how the world is organized. Studies in adults have compellingly demonstrated that sleep after learning new materials supports the consolidation of this information in memory, thereby generating stable and long-lasting memory representations (Diekelmann and Born, 2010; Stickgold, 2005; Peigneux et al., 2001). Infants and children do not only learn much

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but also sleep longer and more deeply than adults (Campbell and Feinberg, 2009; Ohayon et al., 2004). Importantly, children spend a particularly long time during sleep in slow wave sleep (SWS), i.e., a sleep stage that in adults has been revealed to causally contribute to the consolidation of memories (Marshall et al., 2006; Rasch et al., 2007). Considering the immense plasticity of the developing brain together with its specific sleep architecture, children might represent a promising model to further our understanding of the fundamental principles and mechanisms underlying sleep-dependent memory consolidation, although some of these mechanisms may be specific to the conditions during development and cannot be generalized to the adults' brain. This review aims at discussing recent studies investigating the role of sleep for processes of memory consolidation in children and infants. In so doing, we will contrast findings in children with those in adults, keeping in mind the question "What can we learn from children?"

2. Sleep-dependent memory consolidation in adults – current state of knowledge

Since almost 100 years it is well-known from experimental psychological research that sleep benefits the consolidation of memory in adults (Jenkins and Dallenbach, 1924; Heine, 1914). As a standard design in these studies, subjects learn memory materials (encoding) and retrieval of the encoded memories is tested after retention interval of a specific length filled with either sleep or wakefulness. Comparing the retrieval performance when subjects had slept after learning with that after they had stayed awake during the retention interval generally reveals better performance in the sleep condition (Diekelmann et al., 2009; Stickgold, 2005; Peigneux et al., 2001; Rauchs et al., 2005). Sleep-associated improvements in the retention of memories were reported for a great variety of declarative (e.g. learning of paired associates, texts, object locations) and procedural memory tasks (e.g. finger sequence tapping, mirror tracing; for review see Stickgold, 2005; Peigneux et al., 2001; Born and Wilhelm, 2011).

In one of the first studies on processes of sleep-dependent memory consolidation, by Jenkins and Dallenbach (1924), better memory for nonsense syllables after retention sleep than wakefulness was reported. Those authors assumed that sleep benefits performance by protecting newly encoded memories from retroactive interference (Jenkins and Dallenbach, 1924). Specifically, it was assumed that during sleep there is no further entry and encoding of new information into the brain which, during wakefulness, would disturb the consolidation of the formerly encoded memories by overwriting respective representations. Recent theories have proposed that sleep does not only passively protect memories from retroactive interference but enables processes that actively enhances specific memories (Ellenbogen et al., 2006a; Stickgold, 2005; Born et al., 2006; Marshall and Born, 2007). This theorizing arose from the so-called 'standard consolidation theory' that is based on a two-stage model of memory comprising a temporary and a long-term store (Marr, 1971; McClelland et al., 1995). The active system consolidation theory of sleep-dependent memory consolidation postulates that memories initially encoded in the hippocampus which serves as a temporary store for declarative memories, are reactivated during sleep in order to be gradually redistributed preferentially to neocortical sites which serve as long-term store for declarative memories, whereby these memories are incorporated into the pre-existing network of long-term memories (Fig. 1). While most memories during this redistribution process become less dependent of hippocampal circuitry, genuinely episodic memories probably remain anchored in hippocampal networks, as specified in the multiple trace theory of memory consolidation (Winocur et al., 2010; Nadel et al., 2000). Empirical evidence for a neuronal redistribution in the representation of memories that is induced by sleep was provided by studies demonstrating that, compared with wakefulness, sleep after learning declarative materials produced a distinctly greater activation of mid-prefrontal regions at a later retrieval (Gais et al., 2007; Takashima et al., 2006). The theory assumes that the redistribution of neuronal memory representations during sleep is invoked by the repeated reactivation of newly encoded representations. Reactivations of new neuronal representations, representing a basic mechanism of offline memory consolidation, have been demonstrated in a number of studies in rats, where they occurred almost exclusively during SWS and rarely during REM sleep (Pavlides and Winson, 1989; Wilson and McNaughton, 1994; Skaggs and McNaughton, 1996; Ribeiro et al., 2004; Ji and Wilson, 2007; O'Neill et al., 2010). Specifically these studies demonstrated that firing patterns that were present in neuronal assemblies in the hippocampus during the exploration of a novel environment were reactivated in the same sequential order during subsequent SWS. Sleep-dependent neuronal reactivations were also found in birds learning a tutored song, which presumably represents a procedural type of learning (Margoliash and Schmidt, 2010). The neuronal replay observed in adult birds during nocturnal sleep after presenting the tutored song preceded specific changes in the bird's song performance occurring the first time on the next day (Shank and Margoliash, 2009; Dave and Margoliash, 2000). Rasch et al. (2007) demonstrated that reactivations of hippocampus-dependent memories during SWS are indeed causally linked to the consolidation of declarative memory during sleep. They showed in humans that retention of spatial memories (for card-pair locations) was enhanced after experimentally inducing the reactivation of these memories by re-exposing the subjects with memory-associated odors during SWS (Rasch et al., 2007). Exposure to the odor-cues during SWS was associated with an enhanced activation of the left anterior hippocampus confirming that odor presentation indeed reactivated the hippocampal representations (Rasch et al., 2007). Reactivations during sleep also effectively enhance spatial memories when induced by the presentation of auditory cues during SWS (Rudoy et al., 2009).

System consolidation during sleep is assumed to rely on a dialog between hippocampus and neocortex under control of the EEG slow oscillations (~ 0.75 Hz) that characterize SWS and are mainly generated in the neocortex where they originate mostly from frontal cortex areas (Massimini et al., 2004; Murphy et al., 2009). The slow oscillation temporally groups neuronal activity into global up states with wake-like levels of firing activity, and down states of neuronal silence (Steriade et al., 1993). Neuronal reactivations of memory representations in the hippocampus are associated with the occurrence of so-called sharp wave-ripples. The top-down driving influence of the depolarizing up-state of slow oscillations on both the generation of hippocampal sharp-wave ripples and thalamo-cortical spindles synchronizes the occurrence of memory reactivations (and associated ripples) in the hippocampus to the occurrence of ripples forming so-called spindle–ripple events (Clemens et al., 2011; Ji and Wilson, 2007; Sirota et al., 2003; Siapas and Wilson, 1998). Spindle–ripple events have been proposed as a mechanism for the facilitation of the integration of reactivated hippocampal memory information into neocortical storage sites (Fig. 1; Mölle and Born, 2009; Diekelmann and Born, 2010). The importance of slow oscillations and spindles for processes of memory consolidation has been confirmed in a number of recent studies in adults (Wilhelm et al., 2011; Gais et al., 2002; Mölle et al., 2009; Marshall et al., 2006).
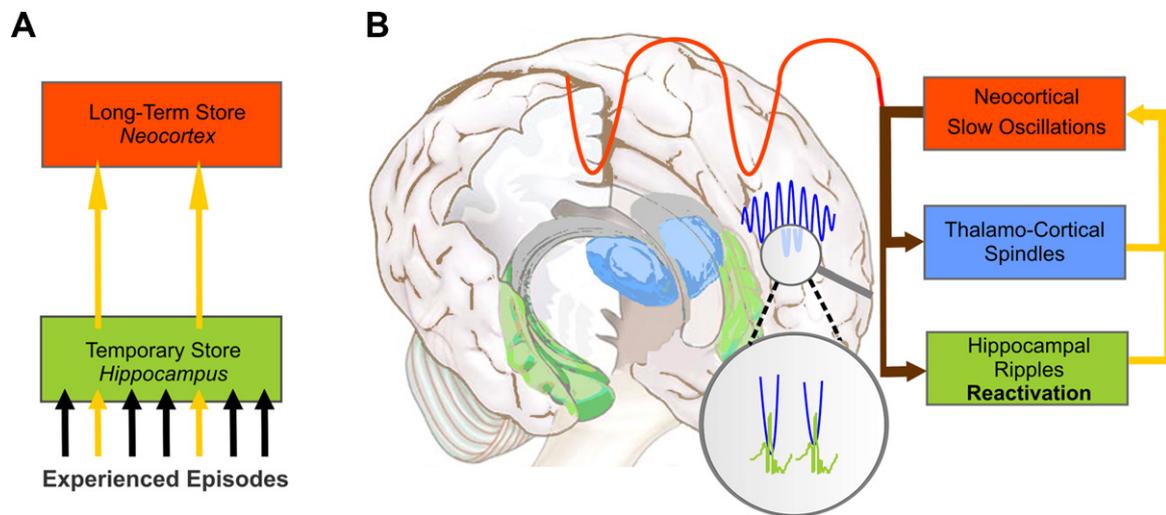
Fig. 1. Active system consolidation during sleep. (A) During slow wave sleep (SWS) memories newly encoded into a temporary store (i.e., the hippocampus in the declarative memory system) are reactivated to be redistributed to the long-term store (i.e., the neocortex). (B) System consolidation during SWS relies on a dialog between neocortex and hippocampus under top-down control by the neocortical slow oscillations (red). The depolarizing up phases of the slow oscillations drive the repeated reactivation of hippocampal memory representations together with sharp-wave ripples (green) in the hippocampus and thalamo-cortical spindles (blue). This synchronous drive allows for the formation of spindle–ripple events where sharp-wave ripples and associated reactivated memory information becomes nested into single troughs of a spindle (shown at larger scale). Spindle–ripple events are considered a mechanism that supports the integration of reactivated memory information into the neocortex. Adapted from Born and Wilhelm (2011).

## 3. The role of sleep on processes of memory consolidation in children and infants

3.1. Declarative memory

Declarative memories are memories for facts and events that are explicitly encoded and later on can be consciously recollected. Encoding of declarative memory during the initial learning episode is thought to essentially rely on the hippocampus and closely connected regions of the medial temporal lobe (Squire et al., 1993; Eichenbaum, 2006). It is well known that sleep changes fundamentally during development (Ohayon et al., 2004; Grigg-Damberger et al., 2007). Importantly, amplitude and slope of slow waves as well as slow wave activity (SWA; EEG spectral power between 0.5 and 4 Hz, including both <1 Hz slow oscillation and 1–4 Hz delta activity) increases until the beginning of puberty at the age of 10–12 years and remarkably decreases thereafter (Jenni and Carskadon, 2004; Campbell and Feinberg, 2009; Kurth et al., 2010). Because SWA was shown to be causally related to the consolidation of declarative memory material in adults (Marshall et al., 2006; Rasch et al., 2007; Mölle et al., 2009), it was hypothesized that the effect of sleep on the consolidation of declarative memories might be even greater in children.

A first study of sleep-associated declarative memory consolidation tested 9–12 years old children on two conditions: In the sleep–wake condition, the children learnt 40 word-pairs in the evening and cued recall was tested the first time in the next morning after a 12-h retention interval of nocturnal sleep, and a second time in the next evening after a second 12-h retention interval filled with daytime wakefulness (Backhaus et al., 2008). In the wake–sleep condition, children learnt the task in the morning and recall was tested first in the following evening and again, after nocturnal retention sleep, in the next morning. Recall of the word memories was significantly improved after the sleep retention intervals, independently of whether sleep occurred immediately after learning (sleep–wake condition) or after a period of daytime wakefulness (wake–sleep condition; Fig. 2). In the latter condition, retention sleep produced a significant gain in the number of recalled word pairs when retrieval performance after sleep was compared with that before. Retention of word-pairs across the sleep interval was positively associated with the time spent in non-rapid eye movement (REM) sleep and negatively related to the time in REM sleep during the night, in both the sleep–wake and wake–sleep condition (Backhaus et al., 2008). The beneficial effect of sleep on the consolidation of declarative materials in children was confirmed in a later study testing visuo-spatial memories in a 2D object-location task similar to the game "Concentration" (Wilhelm et al., 2008). Remarkably, although in those latter experiments, the amount of SWS during the experimental nights was on average more than twofold higher in the children than in the adults, the size of the sleep effect on memory retention was closely comparable between both age-groups. In rats, the process of system consolidation is boosted by the presence of an associative schema in long-term memory, into which new information can be integrated (Tse et al., 2007, 2011). Hence, it could be argued that children, despite higher amounts of SWS, do not show superior declarative memory consolidation because of the presence of fewer schemata and knowledge in long-term memory available to adapt the newly learnt information. Thus, it remains open whether or not the effect of sleep on consolidation of declarative memory, due to the preponderance of SWS, is stronger in children than in adults. To explore this issue, studies need to be performed comparing sleep-dependent memory consolidation in children and adults with task material that is as novel for adults as it is for children.

In contrast to adults, the adolescent's brain seems to be highly capable of compensating for effects of sleep restriction, possibly by flexibly increasing the depth of sleep during the remaining sleep period (Voderholzer et al., 2011). In this study, 14–16 years old adolescents were tested for impairments in sleep-dependent declarative (lists of word-pairs) and procedural memory consolidation (mirror tracing task) as well as for executive functions (i.e. divided attention, working memory, psychomotor speed) during restriction of sleep to up to 5 h on 4 consecutive nights. Performance in all these tasks was not affected by the experimental sleep curtailment, neither after 2 nights of recovery sleep nor after 4 weeks, excluding any short or long-term effect of sleep restriction on memory consolidation. However, the adolescence showed also a remarkable increase in the proportion of SWS during this period which could have nullified effects of reduced sleep time.
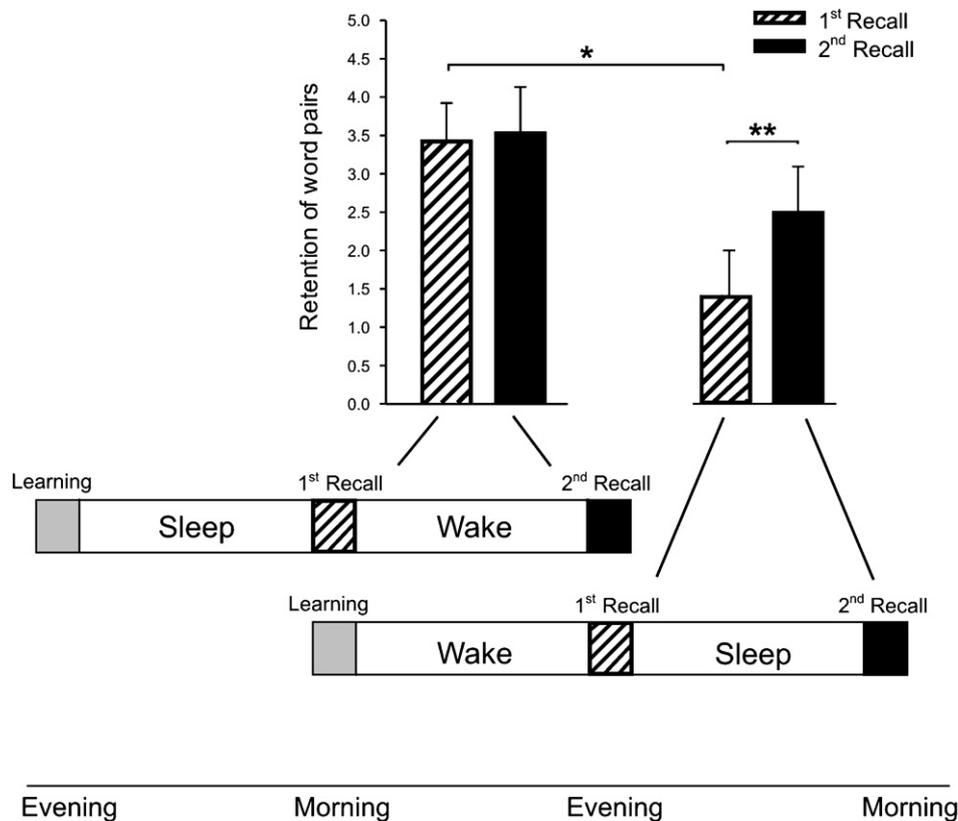
Fig. 2. Sleep-dependent declarative memory consolidation in children. Declarative memory was tested using the word paired associates task (consisting of 40 word-pairs). During learning, the word-pairs were presented on a computer screen, which was followed by a cued recall test. Presentation of the word-pairs was repeated until a learning criterion of 50% correctly recalled word-pairs was reached. Bottom panel illustrates procedure: in the sleep–wake condition, children learned the word-pairs in the evening before sleep and delayed recall was tested first the next morning after a retention interval of nocturnal sleep, and a second time in the following evening after a retention interval of daytime wakefulness. In the wake–sleep condition, children learned the word-pairs in the morning and delayed recall was tested first in the next evening after a retention interval of daytime wakefulness, and then the second time in the next morning after a sleep retention interval. Only during the learning phase, but not at the 1st or 2nd delayed retrieval test, children received feedback upon their response by subsequent presentation of the correct response word (for 1 s). Top bar graphs show results: Performance at the 1st recall test was significantly better when this occurred after a sleep retention interval than after a wake retention interval. Performance at the 2nd recall test significantly increased retention performance (with reference to performance at 1st recall) only when the retention interval between both recall tests was filled with sleep, but not if the children remained awake in this interval. Retention performance is indicated by the difference in correctly recalled words at the 1st/2nd recall minus the number of words recalled at the criterion trial during learning.

Data are from Backhaus et al. (2008).

3.2. Emotional memory

We refer here to emotional memories as memories for events, which are associated with an affective response (e.g. negative or positive feelings, facial and bodily responses). Encoding of such memories typically involves the amygdala, in addition to the hippocampus-dependent declarative memory system. A preferential storage of emotional memory contents is highly adaptive in order to avoid possibly threatening situations in the future. Emotional events are encoded more deeply than neutral events, and from studies in adults there is also evidence that the consolidation of emotional memories during sleep is superior to that of neutral materials, indicating that sleep is actively involved in the selection of highly relevant memories (Wagner et al., 2001; Payne et al., 2008; Hu et al., 2006).

In a first developmental study, Prehn-Kristensen et al. compared the effects of sleep on emotional and neutral memory consolidation in a group of healthy 10–12 years old children and adults using pictures from the International Affective Picture System (IAPS). In line with the above mentioned studies in adults, sleep preferentially benefited recognition memory for emotionally arousing pictures whereas in both age groups the effects of sleep on recognition of neutral pictures was negligible when compared with wakefulness

during the retention interval. Importantly, the emotional enhancement (i.e., the superior retention of emotional over neutral items) was even greater in children than in the adults indicating that the selection of relevant memories during sleep is even more effective during early life (Prehn-Kristensen et al., unpublished results). That in these studies contrasting the effects of sleep on emotional versus neutral memories the effect of sleep on consolidation of neutral materials often failed to reach significance should not be used to infer that the strengthening effect of sleep on these neutral memories is of a small magnitude in general. In fact, such results rather point to a trade-off accompanying sleep's selectivity in memory consolidation such that when overnight retention is tested for neutral and emotional memories simultaneously, the preferential enhancement of emotional memory by sleep in parallel produces a diminution of the effect on the neutral material.

3.3. Procedural memory

The majority of developmental studies concerned with the effects of sleep on memory consolidation examined procedural memories. Procedural memories are memories for skills and habits that are acquired through repeated practice, and basically belong to the category of non-declarative memory (Squire and Zola, 1996;

Cohen and Squire, 1980). Sensorimotor skills form a major part of everyday life activities like writing, riding a bicycle, driving a car and playing a music instrument, with some of these basic skills being acquired during early development like learning to walk and to speak. A great number of studies in adults demonstrated that sleep after training a new motor skill benefits its consolidation as indicated behaviourally by a gain in skill performance (i.e., a faster and more accurate performance at retest compared to performance before sleep) and by a stabilization of the skill memory against disturbing influence of training a similar interfering task (Fischer et al., 2002; Korman et al., 2007; Ellenbogen et al., 2006b; Plihal and Born, 1997).

Fischer et al. (2007) compared the effects of sleep on motor skill memory in a sample of 7–11 years old children and adults, using the serial reaction time task (SRTT, Fig. 3). The SRTT requires the subject to press as fast as possible a repeated cued sequence of buttons while the subject is not aware of the underlying sequence grammar, i.e., that the cued sequence follows distinct regularities. Learning the sequence is thus implicit and manifests itself in faster reaction times to cues that follow the sequence grammar compared to reaction times to a random sequence of cues. Astonishingly, in the children, sleep did not support but instead even impaired skill performance on the SRTT, indicating an impairing effect on the sensorimotor representations underlying the implicit sequence knowledge (Fischer et al., 2007). Following the wake retention period, implicit performance on the SRTT remained unchanged. This pattern clearly differed from that in adults who significantly improved in implicit SRTT performance across overnight sleep but showed deteriorated performance after the retention period of wakefulness. Two recent studies (Prehn-Kristensen et al., 2009; Wilhelm et al., 2008), confirmed this lack of sleep-dependent gain in implicit motor performance in children, using two other procedural tasks which in adults are well-known to profit from post-learning periods of sleep, i.e. the finger sequence tapping task and the mirror tracing task (Walker et al., 2003; Plihal and Born, 1997). The absence of a sleep-dependent gain in skill memories in children is the more striking as the neuroanatomical structures underlying procedural memory formation mature quite early during development, i.e., within the first 3 years of life (Casey et al., 2005; Gogtay et al., 2006).

Interestingly, a lacking gain in sensorimotor performance across sleep has been also revealed in studies of juvenile birds (zebra finches) learning a tutored song (which is an animal model of language learning; Deregnaucourt et al., 2005). Compared with song performance in the evening, the juvenile birds showed more variable and deteriorated song performance in the morning after sleep, and the birds regained original performance levels only after substantial practice during daytime. Adult birds that were kept in acoustic isolation until training started at day 90 after hatching did not show this sleep associated deterioration in song performance. Surprisingly, in the juvenile birds those showing acutely the greatest morning deterioration in performance in the beginning of the 3-months study period, were those which achieved the best song performance at the end of the study period, indicating that the deterioration of song performance in the morning after sleep is linked to some kind of song-memory forming process during sleep. In adult birds, neurons of premotor and motor structures of the bird's vocal song control system, i.e. the nucleus HVC and the robust nucleus of the arcopallium (RA) show replay of the tutored song during sleep that produces changes in the song representation as well as in subsequent song performance the next day (Shank and Margoliash, 2009), and basically similar adaptive processes may occur upon replay activity during sleep in juvenile birds although, along with the deterioration in song structure, HVC neurons show a general decline in burst activity across sleep in juvenile birds (Day et al., 2009). Importantly, replay activity in premotor neurons of the song

control system appears to be driven not only by activity related to the sensory template of the tutor song but also by the auditory feedback from the bird's own singing, as replay is drastically reduced in surgically muted birds. Offline reprocessing in sensorimotor nuclei during sleep may become necessary because of the inability of premotor and motor regions of the song control system to acutely integrate the two types of complex sensory inputs, i.e., the tutored song and feedback from the bird's own singing (Margoliash and Schmidt, 2010; Gobes et al., 2010; Konishi, 2004). Because early reactivated sensory representations and sensorimotor feedback as experienced during actual singing are poorly correlated during song development in juvenile birds, the replay occurring in the absence of supervision by any immediate actual auditory song feedback may manifest itself in a deteriorated song performance in the morning after sleep. This view also implicates that the overnight deterioration in song performance observed only in young birds, is at least partially due to a less established sensorimotor integration in young birds preventing an immediate fine-tuning of premotor and motor representations on the basis of feedback signals from the bird's own song behavior, neither acutely during wakefulness nor at replay during sleep. For a similar reason, i.e., due to basically diminished capabilities to immediately and accurately integrate complex sensory and sensorimotor inputs into premotor programs, sleep-associated reactivations, in the beginning of training, may also fail to produce overnight gains in skill performance during development in humans. Recent data in humans indicate that sleep indeed produces a significant enhancement performance on a motor finger sequence tapping task after the children had received an extended pre-training over several days (Wilhelm et al., in press). Thus, the capability to further improve motor performance by the off-line integration of sensory and sensorimotor inputs into premotor programs might essentially depend on the presence of already quite elaborate representations. A related yet unresolved question in this context is, whether in children, like in zebra finches (Deregnaucourt et al., 2005), a stronger sleep-induced disturbance of skill at an early stage of training, is predictive for a higher level of performance that is achieved at a later stage of training.

3.4. Extraction of explicit knowledge from procedural skill

Taken together, the data discussed in the foregoing section consistently indicate that procedural memories are differentially processed in children and adults, although researchers are far from understanding the underlying mechanisms. Whereas sleep-induced deteriorations in song performance in juvenile birds were related to the developmentally diminished capabilities to accurately integrate complex sensory (feedback) inputs into the song motor representation, in children lacking performance gains after sleep were ascribed to a strong competitive interaction between explicit (i.e., declarative) and implicit components within a motor task in children (Fischer et al., 2007; Wilhelm et al., 2008). Whereas procedural memories were originally conceptualized as being completely independent of any consciousness; i.e., they are implicit (Squire and Zola, 1996; Cohen and Squire, 1980), more recent studies indicate that explicit and implicit aspects operate in parallel in motor memory tasks (Schendan et al., 2003; Shanks and Johnstone, 1999; Willingham, 1998; Ashe et al., 2006). Explicit knowledge can deteriorate implicit task performance manifesting itself in a slowing of reaction times preferentially at the earlier stages of motor learning, when a task is difficult or when cognitive resources are less available. This competitive interaction between explicit declarative and implicit procedural task aspects was found during acquisition (Fletcher et al., 2005; Poldrack et al., 2001; Albouy et al., 2008; Stefaniak et al., 2008), but it can extend to processes of memory consolidation (Brown and Robertson, 2007a,b; Robertson, 2009) and also affects retrieval (Wagner et al., 2004;
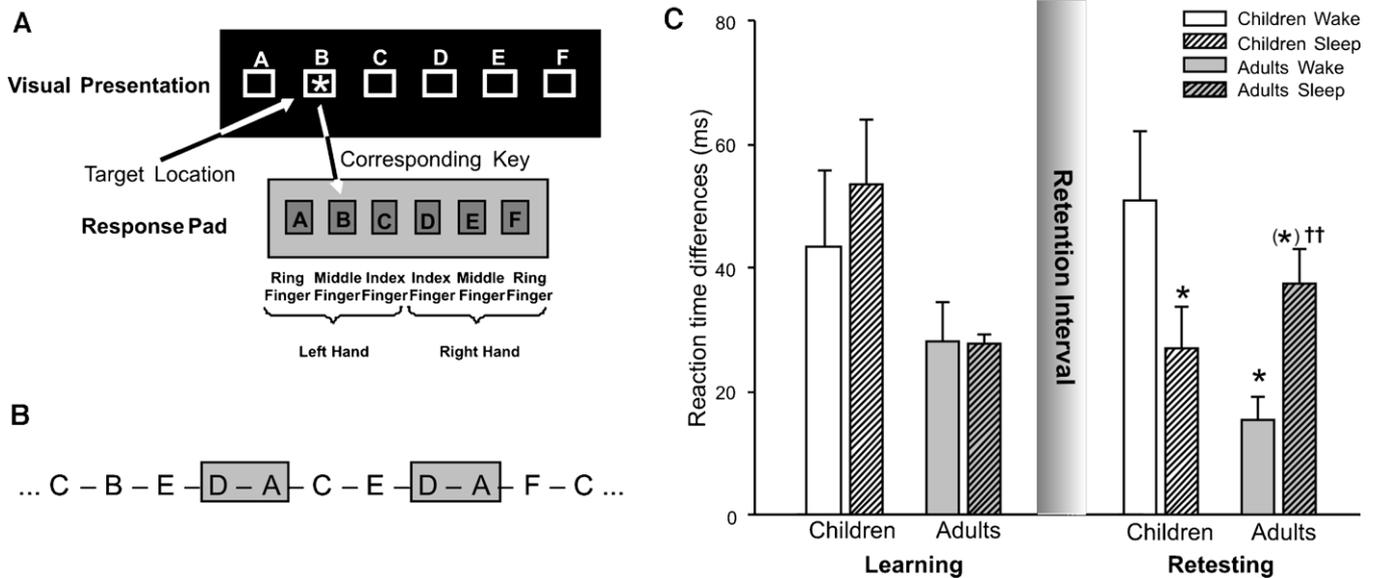
Fig. 3. Sleep-dependent procedural memory consolidation in children and adults using the serial reaction time task (SRTT). (A) On the SRTT subjects were presented six horizontally arranged white boxes. The target cue consisted of a white star, which successively appeared in one of the boxes following a repeated 12-element probabilistic sequence. The subject's task was to react as fast and as accurately as possible to each target position by pressing the spatially corresponding response key, as soon as the cue was presented. (B) The sequence of target locations was based upon a set of probabilistic rules such that each of two successive target locations constituted the temporal context that legally could be followed by one of two possible target locations, each occurring with a probability of 50%. In the illustrated example sequence the temporal context 'D', 'A' (gray fields) could be legally followed by position 'C' or 'F'. (C) SRTT performance before (learning) and after (retesting) retention intervals of sleep and wakefulness in children and adults. At learning, subjects performed two blocks of 194 target positions, each containing 15% non-grammatical target positions. Bars represent, as a measure of implicit knowledge of the sequence grammar underlying the SRTT, mean reaction time differences between grammatical and non-grammatical target positions. This reaction time difference was significantly decreased at retesting (with reference to performance at learning) when children had slept during the retention interval, indicating that sleep deteriorated implicit sequence knowledge in the children. By contrast, in adults sleep during the retention interval improved implicit sequence knowledge. The wake retention interval did not affect implicit sequence knowledge in children, but in adults distinctly diminished implicit sequence knowledge at retesting. $*p < 0.05$, $(*)p < 0.07$ compared with performance at learning, $\dagger\dagger p < 0.01$ compared with the wake condition.
Data are from Fischer et al. (2007).

Fischer et al., 2006). Because of their great amounts of SWS, sleep in children might preferentially strengthen hippocampus-dependent explicit aspects in a skill representation thereby crucially disturbing implicit aspects. In a recent study, we tested this hypothesis using a coarse motor memory task resembling the SRTT, i.e. the 'button-box task' (Wilhelm et al., submitted for publication). During the learning session taking place under implicit conditions, children and adults repeatedly pressed a sequence of buttons according to an underlying 8-elements sequence, without being aware of this sequence. After a night of sleep or after a parallel daytime wake interval, the subject's explicit knowledge about the SRTT sequence was explored using a generation task where the subject was asked to point at the buttons in the order they were cued at the original SRTT training (under implicit conditions). The number of correct transitions from one to the next button predicted on this generation task was used as measure of explicit sequence knowledge. Sleep benefited the generation of explicit knowledge in both age-groups. However, this benefit was strikingly greater in children than in adults. Importantly, explicit knowledge after sleep in children was also profoundly enhanced in comparison to what a control group of children showed when tested immediately after training, indicating that it is indeed sleep which supports the extraction of explicit from implicit knowledge. Superior explicit knowledge after sleep correlated with the amount of SWA in both age groups.

These findings are well in line with a previous study in adults showing that those subjects who slept after implicitly practicing an arithmetic number reduction task comprising a hidden rule, at a later re-test gained insight into this hidden rule with a twofold higher probability than subjects who had stayed awake after practicing the task (Wagner et al., 2004). The emergence of insight into this task is promoted by SWS-rich early nocturnal sleep in adults rather than by late REM-rich sleep, indicating that SWS is critically involved in the extraction of explicit knowledge (Yordanova et al., 2008).

The learning of language and underlying grammar in infants is a process that shares essential features with the sleep-induced extraction of regularities and rules observed in tasks like the SRTT. Recent studies have provided first evidence that sleep preferentially supports the extraction of grammatical aspects rather than the memory for words in language learning infants. Gomez et al. (2006) familiarized 15-months old infants in a learning phase with auditory strings of words of an artificial language. The infant's orienting response, i.e. turning his/her head toward familiar and unfamiliar strings, was used to assess delayed retrieval. Compared to a non-napping control group, children who had napped after learning appeared to be more able to abstract a rule-like pattern underlying the strings of words. However, signs of correct remembering of the presented words were enhanced in the wake group (Gomez et al., 2006). The authors replicated and extended these results in a second study employing the same task and the same study design but a retention interval of 24 h (Hupbach et al., 2009). Although orienting is a well-known hippocampus-dependent function (Sokolov, 1975), it remains to be elaborated to what extent the sleep-induced extraction of grammatical structure in infants involves the hippocampus-dependent declarative memory system.

Overall, the findings indicating a facilitating effect of sleep on the generation of hippocampus-dependent explicit knowledge from an implicitly learned motor task are in line with the general assumptions of system consolidation theory as specified by the more recently proposed 'transformation hypothesis' (Frankland and Bontempi, 2005; Winocur et al., 2010; Diekelmann and Born, 2010). This theory postulates that newly acquired memories are initially stored into a temporary buffer, i.e., the hippocampus in the declarative memory system. During sleep – and here in SWS – these

memories are reactivated to be redistributed and integrated with the existing network of memories within the neocortex. In the process of system consolidation fresh memory representations are not only strengthened but also become qualitatively transformed and reorganized (Born et al., 2006; Payne and Kensinger, 2010). During SWS memory reactivations spreading from hippocampus toward the neocortex might mediate a restructuring of the representation so as to produce an increased binding into neocortical, particularly prefrontal circuits (Frankland and Bontempi, 2005; Darsaud et al., 2011) and such restructuring might in fact underlie the sleep-dependent generation of explicit knowledge. Thus, sleep does not only strengthen a memory representation in the way it exists but, by extracting invariant and relevant features of the representation and its adaptation to pre-existing schemata, brings about changes in its quality, with this effect being greater during childhood than adulthood.

3.5. Wake consolidation and the role of the pre-sleep performance level

It could also be argued that the missing sleep-induced gain in motor performance in children does not primarily reflect an altered consolidation during sleep but is due to an enhanced capacity to consolidate newly acquired memories during wakefulness, as respective studies often compare retention performance after sleep with those after wake retention intervals. Evidence in support of this view came from a recent study testing the stability of newly encoded motor memories after wake retention intervals in different age groups (Dorfberger et al., 2007). In children (aged 9 years) newly acquired finger sequence tapping representations after a 2-h wake retention period were less susceptible to interference from learning a different sequence than in adolescents (aged 17 years) or adults, indicating that processes of motor memory consolidation during waking follow rather fast kinetics in children. However, this study did not compare the stabilization of motor memories during waking with that after retention intervals of sleep, which prevents any conclusions with regard to differential effects originating from the two brain states. In fact, observations in adults suggest that the process of stabilizing a motor representation is even further accelerated by sleep, compared with wakefulness (Korman et al., 2007).

Motor performance in children is much slower and less automated than in adults (Thomas et al., 2004; Fischer et al., 2007; Dorfberger et al., 2007). This is of importance because the performance level at learning has repeatedly been shown to modulate processes of sleep-dependent memory consolidation in adults. Intermediate performance levels are considered most effective in this context (Diekelmann et al., 2009; Albouy et al., 2008; Kuriyama et al., 2004). Against this background, a basic question arises about the nature of the lacking sleep-induced gain in motor performance in children: does this missing profit from sleep represent an ubiquitous and unchangeable characteristic of the immature brain, or does it depend on behavioral features specifically linked to a task in which children are usually less experienced but which can be modified by training. The later alternative predicts that sleep would be beneficial to motor memories also in children if pre-sleep performance can be enhanced to a level comparable with that in adults. Hence, the purpose of a recent study was to compare motor skill across 120-min retention periods of sleep and wakefulness in children (aged 4–6 years) after experimentally increasing performance at learning by manipulating the amount of training (Wilhelm et al., in press). In two corresponding control groups of adults, motor performance was either kept at a low level by restricting the amount of training to a minimum, or brought to a quite high performance level by providing increased amounts of training. Results confirmed that sleep supports the gain in motor performance at an intermediate performance level, i.e., in children after high amounts of training and in adults after restricted training. However, sleep did not improve skill performance in children whose pre-sleep performance was kept at a low level or in highly trained adults (Fig. 4). Getting back to the initial question, these data indicate that the lacking gain in motor performance which was found in the first studies in children is not a general phenomenon inextricably linked to the developing brain but is due to a currently low level of performance on a specific task. It seems that motor performance in children only after extensive training reaches a level of strength at which sleep-dependent benefits directly translate into benefits in skill and reaction times rather than in a disruption of skill due to a predominant gain in explicit task knowledge.

4. Sleep-dependent memory consolidation in children suffering from ADHD

4.1. Why studying sleep-dependent memory consolidation in ADHD patients?

The key symptoms in patients suffering from attention-deficit/hyperactivity disorder (ADHD) are inattention, hyperactivity and impulsivity (American Psychiatric Association, 2000). The sleep architecture in terms of the macro structure of sleep appears to be not consistently altered in children with ADHD (Cortese et al., 2009), although these patients often experience multiple sleep disturbances, such as delayed sleep onset, sleep or bedtime resistance, prolonged tiredness upon waking and daytime sleepiness (Cortese et al., 2009; Konofal et al., 2010). When experimentally invoked in healthy subjects, such alterations of sleep can induce ADHD-like behavior, indicating that sleep disturbances might contribute to the maintenance of ADHD (Gruber et al., 2011; Paavonen et al., 2009; Steenari et al., 2003). The primary cause of the disease, however, is a malfunction of the prefrontal cortex. There is convergent evidence from a great number of imaging and neuropsychological studies indicating a profound deficit in the prefrontal cortex together with striatal brain regions in patients with ADHD. This deficit, amongst others, expresses itself in a volume reduction and decreased activation in these regions during task execution (Bush et al., 2005; Rubia et al., 1999; Shaw and Rabin, 2009; Zang et al., 2005). On the background of this evidence, ADHD can serve as a model to scrutinize the contributions of the prefrontal cortex to sleep-dependent memory consolidation.

Based on studies in healthy adults, it was argued that the prefrontal cortex during the encoding of memories in the wake phase is involved in a tagging of those memories that are relevant for the subject's future and, therefore, are preferentially consolidated for the long-term during subsequent sleep (Diekelmann and Born, 2010; Wilhelm et al., 2011). This in mind, it can be hypothesized that such tagging of memories is diminished in ADHD patients and that consequently sleep in these patients does not adequately discriminate between relevant and less relevant memories. Given that the frontal cortex is also the main source of slow oscillations which hallmark the EEG during SWS (Massimini et al., 2004; Murphy et al., 2009) the study of ADHD patients can additionally provide important information on the role of this sleep stage for the consolidation of declarative and procedural memories. Although the total time spent in SWS during the night does not differ between ADHD patients and healthy subjects, its stability as reflected by the cyclic alternating pattern in slow wave activity appears to be reduced (Miano et al., 2006), and specific features such as amplitude and functionality of slow oscillations might be altered in these patients although this has not been thoroughly studied so far.
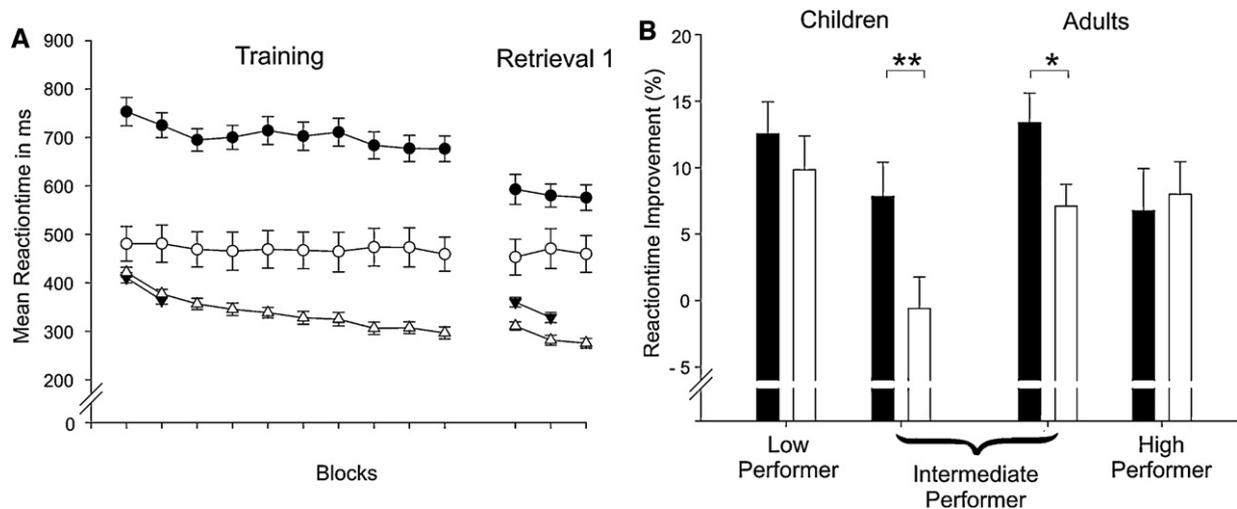
Fig. 4. Sleep-dependent motor memory consolidation at different amounts of training on the button-box task. The button box is a white 50 cm × 22 cm × 7 cm box with eight colored buttons placed on its upper panel in two rows that are consecutively flashed up according to a repeating 8-elements sequence. Subjects were instructed to press the button flashing up as fast as possible. Each block during training and retrieval testing consists of five sequences with a 20-s break between blocks during which the subject received feedback on his/her individual performance level during the preceding block. (A) Motor performance in low-performing and intermediate-performing children (filled and open circles, respectively) and intermediate-performing and high-performing adults (filled and open triangles, respectively) during training and first retrieval (Retrieval 1) that took place 30 min after the training phase. The amount of finger tapping training received before the experimental retention interval was in low-performing children 13 30-s blocks, in intermediate performing children 33 blocks, in intermediate performing adults 13 blocks, and in high performing adults 4 blocks. (B) Motor memory consolidation. Gains in motor performance after 2-h retention intervals filled with sleep (black bars) and wakefulness (white bars) in low-, intermediate- and high-performing subjects indicated by the percent difference in performance between a first retrieval test before the retention interval and a second retrieval test after the retention interval (with performance at the first retrieval set to 100%). $^{**}p < 0.01$, $^{*}p < 0.05$, for pairwise comparisons between sleep and wake conditions. Data are from Wilhelm et al. (in press).
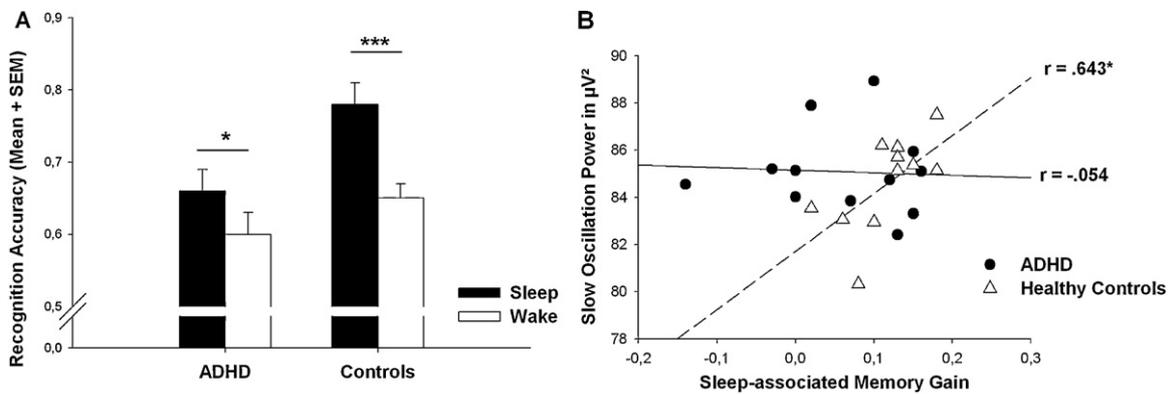
4.2. Sleep-dependent memory consolidation in patients with ADHD

Indeed, consolidation of memory during sleep in ADHD patients appears to deviate from that in healthy controls. We compared the retention of declarative memories for pictures across retention intervals of nocturnal sleep and of daytime wakefulness between ADHD children (aged 10–16 years) and healthy controls (Fig. 5; Prehn-Kristensen et al., 2011a). Retrieval testing following the retention intervals revealed that both subject groups recognized a greater number of previously presented pictures after retention sleep compared to wakefulness. However, the impact of sleep on memory performance was greater in healthy controls than in ADHD patients. Although slow oscillation power during NonREM sleep in the retention intervals did not differ between the groups, a significant positive association of sleep-dependent memory gains with slow oscillation power was observed only in the healthy subjects, pointing toward a reduced functionality of slow oscillations in ADHD.

Whereas the impact of sleep on declarative memories is smaller in ADHD children compared to healthy controls, overnight sleep did benefit procedural motor performance in these patients (Prehn-Kristensen et al., 2011b). In this study, ADHD patients improved in performance on the button-box task to a greater extent after offline periods of sleep compared to wakefulness, whereas motor performance in healthy children did not differ between both conditions. As the benefit from sleep was assessed with reference to corresponding performance improvements across the wake retention interval, which were lower in the ADHD children than controls, this study cannot exclude contributions of an altered wake processing of memories to the pattern of skill performance in the ADHD. Nevertheless, the findings overall indicate that the sleep-dependent consolidation of declarative and procedural memories in ADHD is in stark contrast to that found in healthy children. Indeed, these findings are clearly in line with our view derived from the investigation of healthy children discussed above, namely that the consolidation of both declarative and procedural aspects of memory during

sleep is interlinked. The impaired consolidation of hippocampus-dependent memories during sleep in ADHD patients might reduce the competitive interaction with processes strengthening implicit procedural aspects in the skill representation, thus unmasking the emergent offline gains in procedural motor performance at retest after sleep in these subjects.

Boosting slow oscillations during NonREM sleep in adults by the transcranial application of electrical potentials fields (oscillating at the 0.75 Hz slow oscillations frequency) significantly enhanced the retention of word-pairs the subjects had learned before sleep, indicating that slow oscillations are causally related to processes of declarative memory consolidation (Marshall et al., 2006). In order to investigate the role of slow oscillations for processes of memory consolidation during development, we applied the same protocol of sleep-associated transcranial electrical stimulation in children suffering from ADHD (Prehn-Kristensen et al., unpublished results). Prior to sleep, the children acquired declarative (visuo-spatial object-locations) and procedural memories (finger sequence tapping). Retrieval performance after sleep was compared between slow oscillation stimulation and a sham control condition. Preliminary analyses revealed that in ADHD children, similar to the findings in healthy adults (Marshall et al., 2006), slow oscillation stimulation during post-learning sleep improved retention of declarative memories. Interestingly, with respect to the consolidation of procedural memories, transcranial electrical stimulation simultaneously reduced sleep-induced gains in performance accuracy, compared to the sham condition. These findings suggest slow oscillations might also contribute to the altered processes of sleep-dependent memory consolidation in ADHD (as reflected by inferior sleep-induced changes in declarative memory). The applied electrical stimulation could improve the functionality of slow oscillations thereby normalizing memory consolidation during sleep in ADHD patients toward predominant consolidation of hippocampus-dependent declarative aspects in memory. However, healthy control children were not included in this study rendering these conclusions preliminary.

Fig. 5. Sleep-dependent declarative memory consolidation in young patients with attention-deficit/hyperactivity disorder (ADHD). Twelve patients with ADHD and twelve healthy controls (aged 10–16) were shown two sets of pictures each containing 180 emotional and 180 neutral pictures taken from the International Affective Picture System. During learning (120 pictures) participants had to rate the emotional arousal of the pictures; at a delayed recognition test old (120) and new (90) pictures were presented in random order and the subject had to indicate for each picture whether it was old or new. In the sleep condition, learning took place in the evening and picture recognition was tested in the morning after nocturnal sleep; in the wake condition, learning took place in the morning and recognition was tested after a retention interval of daytime wakefulness. (A) Recognition accuracy in both groups after sleep and wake retention intervals. Although both, ADHS patients and controls improved in recognition accuracy to a greater extent after sleep than wakefulness, the benefit from sleep in recognition accuracy was significantly lower in the ADHD patients compared to the controls. $*p < .05$; $***p < .001$, for comparisons between sleep and wake conditions. (B) Correlations between the sleep-associated enhancement in recognition accuracy (i.e., the individual difference between recognition accuracy in the sleep and wake condition) and slow oscillation power (<1 Hz in μV^2) during NonREM sleep. Bold circles and solid regression line refer to ADHD children; triangles and dashed regression line refer to healthy controls. Only in healthy controls slow oscillation power was correlated with sleep-associated improvement in recognition accuracy. *Note*: correlation coefficients between ADHD and healthy controls differ significantly.

Data are from Prehn-Kristensen et al. (2011a).

Sleep in adults preferentially consolidates memories that are of future relevance possibly by a SWS related reprocessing of these memories (Wilhelm et al., 2011; Fischer and Born, 2009; Diekelmann et al., submitted for publication). As mentioned, this selectivity in memory consolidation during sleep is presumably achieved by a prefrontal marking of hippocampus-dependent memories during encoding, a mechanism that could likewise be involved in the preferential consolidation of emotional over neutral memories during sleep (e.g., Wagner et al., 2001; Payne et al., 2008; Hu et al., 2006). A prefrontal contribution to the enhanced consolidation of emotional materials is in fact indicated by recent experiments in ADHD children who – presumably due to a dysfunctional prefrontal control of memory processing during both encoding and off-line consolidation – did not show the normal sleep-associated enhancement for the consolidation of emotional memories (Prehn-Kristensen et al., unpublished results). Such deficits in the consolidation of emotional memory during sleep might contribute to an exacerbation of symptoms of disruptive behavior disorders (such as conduct disorder, oppositional defiant disorder) often reported in ADHD (Maughan et al., 2004), although this issue requires further studies. Collectively, these studies exploiting ADHD as a model of prefrontal dysfunction support the notion that normal development is characterized by an enhanced consolidation of hippocampus-dependent memory during sleep, whereby the effective regulation of these consolidation processes that take place during SWS, essentially relies on the prefrontal marking of memories to be strengthened by sleep.

5. Conclusion

The studies discussed here confirm the importance of sleep for processes of memory consolidation in children and infants. However, sleep-dependent memory consolidation during development does not appear to be entirely different from that in adults but is based on similar principles. Rather, due to the great amounts of SWS, consolidation during sleep is more efficient. These great amounts of SWS with prevalent EEG slow oscillation activity in children promote the preferential consolidation of memories in the hippocampus-dependent declarative memory system whereby, compared with adults' sleep, sleep in children produces greater

gains of declarative knowledge, which can express in quantitative (increased number of words recalled) and qualitative (enhanced implicit-to-explicit conversion of knowledge) changes in memory performance (e.g., Backhaus et al., 2008; Wilhelm et al., submitted for publication). Investigations in children with ADHD as a model of impaired prefrontal function, do not only underscore the role of SWS for the consolidation of hippocampus-dependent memory but also the contribution of the prefrontal cortex to this process. Explicit encoding of hippocampus dependent memories relies on the prefrontal cortex, which appears to tag these memories during encoding thereby facilitating their access to consolidation during subsequent sleep. In ADHD children, the prefrontal marking of memories during waking or preferential selection of hippocampal memories for consolidation during sleep slow oscillation activity (or both) may be compromised. Accordingly, they show diminished benefits from sleep for declarative memories, and they are also less able to select emotional over neutral memories for consolidation during sleep. On the other hand, ADHD children display a clear sleep-associated benefit for motor skills, which was lacking in healthy children most likely because of the preponderance of declarative memory consolidation. Indeed, findings in healthy children highlight the strong competitive interaction between explicit (declarative) and implicit (procedural) components of a memory representation that persists during the sleep-dependent process of consolidation. Healthy children, due to predominant SWS, show preferential strengthening of declarative aspects in memory, and only at advanced performance levels is there a direct profit of motor skill (Wilhelm et al., in press). This predominant consolidation of hippocampus-dependent declarative memory at the cost of an immediate benefit in procedural skill that is seen during sleep in healthy children finds a striking parallel in juvenile song birds learning a song, whose performance on the tutored song deteriorates across sleep rather than improving (Deregnaucourt et al., 2005). It may in fact point at a principle function of sleep-dependent memory formation as such offline-consolidation may be necessary only in conditions where complex afferent patterns of sensorimotor (feedback) stimulation cannot be effectively integrated online into representations regulating efferent motor behaviors of similar complexity. This is a hypothesis clearly in need of experimental elaboration. However, children and infants who are in the very

beginning of learning complex behaviors, may comprise a very promising model for the study of this hypothesis.

Acknowledgments

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