Pathophysiology of sleep-dependent memory consolidation processes in children

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Cognitive impairments are often associated with abnormal sleep activity in developmental disorders and pathologies of childhood. Besides, accumulated evidence indicates that post-training sleep benefits to the consolidation of recently learned information in healthy adults and children. Although sleep-dependent consolidation effects in children are clearly established for declarative memories, they remain more debated in the procedural memory domain. Nowadays, recent experimental data suggest close interactions between the development of sleep-dependent plasticity markers, cortical maturation and cognition in children. In the present review, we propose that studying sleep and memory consolidation processes in developmental disorders and acquired childhood pathologies can provide novel, enlightening clues to understand the pathophysiological mechanisms subverting the disruption of long-term cerebral plasticity processes eventually leading to cognitive and learning deficits in children.

1. Introduction

Novel information is not immediately stored at the time of learning in its final, enduring form. Rather, fresh memories undergo a series of transformations subordinated by the capacity of the brain to modify its structure and function over time, i.e. brain plasticity (Kolb and Whishaw, 1998). Nowadays, accumulated evidence suggests that post-learning sleep participates in the dynamic consolidation processes by which novel memories are gradually incorporated into pre-existing sets of mnemonic representations (Bontempi et al., 1999; Karni et al., 1998; McClelland et al., 1995) or subjected to forgetting (Peigneux et al., 2010). In children, sleep disturbances have been often considered as the epiphenomena of an underlying maturational disorder leading to cognitive impairments. However, cortical maturation and sleep-dependent mechanisms of brain plasticity follow similar developmental trajectories, suggesting closest interactions between these plastic processes (Buchmann et al., 2011; Kurth et al., 2010b, 2012). In this framework, abnormal sleep activity in children might be a causal, or at least a contributing factor in cognitive and learning impairments (Chan et al., 2011; Van Bogaert et al., 2011). In the present review, we propose that studying sleep and memory consolidation processes in developmental disorders (e.g. specific language impairment) and acquired pathologies (e.g. childhood epilepsies) can provide novel, enlightening clues to understand the pathophysiological mechanisms subverting the disruption of long-term cerebral plasticity processes eventually leading to cognitive and learning deficits.

First, we will shortly introduce the reader to the dominant theoretical models of sleep-dependent memory consolidation and supporting evidences from adult studies, then discuss how sleep-dependent plasticity markers evolve throughout development and interact with cognitive functioning and/or cortical maturation. Second, we will review those studies having investigated sleep and memory consolidation processes in healthy children. We will discuss the specificity of these processes in children as compared to adults, and how their study may deepen our understanding of the fundamental interactions between sleep and memory consolidation mechanisms. Finally, we will review several clinical syndromes associating sleep disturbances and memory consolidation deficits, especially including attention deficit/hyperactivity disorder (ADHD) and idiopathic childhood epilepsy syndromes.

2. Sleep-dependent memory consolidation in adults

Studies conducted in healthy adult participants have provided compelling evidence that sleep actively participates in the consolidation of long-term memories (for recent reviews see Born and Wilhelm, 2012; Diekelmann et al., 2009; Maquet, 2001; Peigneux and Smith, 2010; Stickgold, 2005). In the declarative memory domain (i.e. the memory for facts and events, usually verbalizable and explicit), beneficial effects
of post-learning sleep on performance have been highlighted using mostly verbal (word pairs) and visuospatial (e.g. memory for pictures or objects’ location, virtual navigation) hippocampus-dependent learning tasks. For instance, cued recall of learned pairs of words was consistently shown better after post-learning sleep than after a similar period of time spent awake (e.g. see Fowler et al., 1973; Gais and Born, 2004; Gais et al., 2006; Plihal and Born, 1997, 1999; Wilhelm et al., 2008; for reviews see also Diekelmann et al., 2009; Peigneux and Smith, 2010). Additionally, sleep may help protecting recently learned memories against retroactive interference due to the acquisition of a novel and related verbal material (Ellenbogen et al., 2006, 2009). Therefore, sleep would participate in memory consolidation processes more than by merely protecting novel memories from ongoing, nonspecific daytime interferences and memory decay as previously advocated (Jenkins and Dallenbach, 1924; see also Wixted, 2004).

Likewise in the non-declarative or procedural memory domain, beneficial effects of post-learning sleep have been evidenced for the consolidation of novel skills and habits, although results are more controversial. Sleep-dependent improvements in visual discrimination skills have been consistently demonstrated using the texture discrimination task (TD; Gais et al., 2000, 2008; Karmi et al., 1994; Stickgold et al., 2000). Furthermore in this task, performance deteriorates over repeated practice sessions within a day reflecting the saturation of the underlying neural circuits, unless sleep is allowed between sessions (Mednick et al., 2002). In this case, performance stabilizes or even increases depending on the duration of the sleep episode and the availability of slow wave sleep (SWS) and rapid eye movement (REM) sleep (Mednick et al., 2003). However, results have been less reliable in the perceptual auditory modality, with some studies reporting a positive effect of post-learning sleep for the consolidation of auditory discrimination skills (Gaab et al., 2004) or the generalization of phonological categories (Fenn et al., 2003), and others concluding that post-training time alone (i.e. either sleep or wakefulness) is sufficient for the development of auditory perceptual skills (Collet et al., 2012; Gottselig et al., 2004; Roth et al., 2005). Elementary motor skills also benefit from subsequent sleep, as evidenced using the finger-to-thumb opposition task (FOT) or its variant the finger-tapping task (FTT). Performance in this task is enhanced in the absence of further practice after post-learning sleep but not wakefulness (Fischer et al., 2005; Korman et al., 2003; Nishida and Walker, 2007; Walker et al., 2002, 2003, 2005), or stabilized against the effect of an interfering training on a different motor sequence (Korman et al., 2007). On the other hand, results gained using visuomotor tasks are disputable. Using the rotation adaptation task (Ghilardi et al., 2000), studies found that post-training sleep improves (Hill et al., 2008; Huber et al., 2004) or stabilizes (Albouy et al., 2012) motor adaptation skills, whereas other authors concluded that time alone is actually sufficient to achieve a similar outcome (Debas et al., 2010; Donchin et al., 2010; Huber et al., 2012; Wilbulm and Bontempi, 2005). On the other hand, the synaptic homeostasis theory proposes that the activation of learning-related neural structures during training leads to a local, use-dependent synaptic potentiation phenomenon. Sleep would then globally downscale synaptic potentiation to a baseline level allowing renewed plasticity, indirectly leading to the consolidation of the newly acquired information (Tononi and Cirelli, 2003, 2006).

3.1. The hippocampo-neocortical dialogue

As illustrated in Fig. 1, the hippocampo-neocortical dialogue model proposes that sleep-dependent memory consolidation relies on a complex dialogue between hippocampal and neocortical regions under the feed-forward control of slow oscillations (<1 Hz). These slow oscillations originating in the prefrontal cortex during SWS (Massimini et al., 2004; Murphy et al., 2009) feature a hyperpolarization phase during which neurons are virtually silent (down state), followed by a depolarization phase (up state) during which neuronal activity fires in a micro wake-like activity pattern known to facilitate neuronal interactions (Steriade, 2006; Steriade et al., 1993a, 2001). The succession of hyperpolarization and depolarization phases progressively synchronizes neuronal activity into a unified oscillatory machine encompassing thalamic (Steriade et al., 1993b) and hippocampo-cortical regions (Mölle et al., 2009) known to be crucial in consolidation processes (Born and Wilhelm, 2012). According to this model, the depolarization phase of the slow oscillations is involved in the repeated reactivation of memory traces temporarily stored in the hippocampus, due to the co-activation of thalamo-cortical spindles and fast hippocampal oscillations named sharp-wave ripples (SPWs). This synchronized activity allows the formation of spindle-ripple events into which SPWs and freshly reactivated hippocampal information are combined then transferred to the neocortex during the depolarization phase of the slow oscillation (Clemens et al., 2011; Mölle et al., 2009; Siapas and Wilson, 1998; Siroti and Buzsaki, 2005; Wierczynski et al., 2009). The oscillatory mechanisms by which sleep spindles reach the neocortex may also facilitate the putative gradual integration of reactivated hippocampal information into pre-existing sets of mnemonic representations stored over neocortical regions (Diekelmann and Born, 2010).

The hippocampo-neocortical dialogue model has been widely supported by human and animal studies showing that reactivations of learning-related cerebral activity occur during post-training sleep. Moreover, these reactivations and/or the progressive transfer from learning-related hippocampal to cortico-sub-cortical networks days to months later are specifically involved in sleep-dependent memory consolidation processes. In humans, post-training reactivation of hippocampal activity during non-REM (NREM) sleep or SWS after a spatial navigation task correlates with overnight performance improvement (Peigneux et al., 2004). Furthermore, successful recall of word pairs is associated with a sleep-dependent increase in neuronal activity first in the hippocampus a few days after learning then in the medial prefrontal cortex (mPFC) several months later (Gais et al., 2007; Takahsima et al., 2006). Subsequent studies also found a sleep-dependent hippocampo-cortical or sub-cortical transfer of learning-related neural activity, although sometimes in the absence of overt behavioral changes (Orban et al., 2006; Rauchs et al., 2008; Stepchen et al., 2007; Urbain et al., in press). Additionally, other studies showed that triggering slow oscillations (Marshall and Born, 2011; for a review) or cueing the learned information (e.g. using associated odors or sounds) during post-training SWS strengthens the consolidation of novel declarative memories (Rasch et al., 2007;
The synaptic homeostasis hypothesis (illustrated in Fig. 2) is based on the hypothesis that learning modifies the strength and/or the amount of synaptic connections between neurons (Silva, 2003; Ying et al., 2002). Learning therefore potentiates the synaptic weights in related cerebral networks (Silva, 2003), eventually leading to neuronal saturation or neuronal depression and impaired plasticity. During NREM sleep, low frequency oscillations (slow wave activity [SWA] < 1 Hz) known to induce synaptic depotentiation (Kemp and Bashir, 2001) would homeostatically decrease synaptic weights to baseline level. That is, SWA will be locally higher in learning-related, saturated synaptic networks, eventually allowing renewed plasticity while at the same time consolidating the learned information (Tononi and Cirelli, 2003, 2006). In this framework, synaptic downscaling (or depotentiation) induced by slow oscillations would indirectly lead to memory consolidation.

Huber et al. (2004) have substantiated the synaptic homeostasis theory using high density EEG recording in participants trained to incidentally adapt reaching movements to a systematic deviation of the cursor (i.e. the rotation adaptation task Ghilardi et al., 2000). Results showed not only a sleep-dependent increase of NREM sleep slow oscillations (i.e. SWA) over the right parietal regions (BA 40, BA 7) subtending this visuo-motor adaptation process (Cohen and Andersen, 2002), but also a positive correlation between increased SWA during post-training sleep and overnight gains in performance (Huber et al., 2004). In the framework of the synaptic homeostasis hypothesis (Tononi and Cirelli, 2003, 2006), the overnight gain in performance is indirectly due to the synaptic downscaling process occurring during sleep, decreasing the strength of each synapse by a proportional amount until the total amount of synaptic weights impinging on each neuron returns to baseline level. Less effective synapses contributing to an imprecise movement (i.e. noise) will then reach a threshold of inefficiency and cease to interfere in the execution, indirectly inducing the strengthening of relevant synaptic connections for appropriate movements and improving the signal to noise ratio. Altogether, this theory proposes that the synaptic homeostasis induced by slow oscillations (< 1 Hz) might link cellular mechanisms underlying learning processes.

The hippocampo-neocortical dialogue and the synaptic homeostasis models are not mutually exclusive. In both cases they are based on physiological processes taking place during NREM sleep, which leaves open the question of the modeling of REM sleep contributions in memory consolidation. However, further theoretical advances are also needed, since none of the two theories are currently able to satisfactorily explain all of the experimental observations in the field of sleep and memory. As it stands, the hippocampo-neocortical dialogue theory seems better fitted to explain the sleep-dependent reorganization processes subtending the consolidation of hippocampus-dependent declarative memories, whereas the synaptic homeostasis hypothesis would better explain the consolidation of procedural memories through the optimization of synaptic activity in neocortical regions necessary for learning and subsequent performance. In any case, both theories are “working models” that can be used as reference frames to understand the neurophysiological modifications underlying the evolution of sleep-dependent memory consolidation processes in children and the impairments potentially associated with abnormal sleep activity.

4. Sleep, cognition and memory consolidation processes in childhood

4.1. Cognition-related sleep parameters: developmental features

Childhood is characterized by an intense maturation in sleep regulation processes, especially during the first months of life (Jenni et al., 2004) and until the age of 4–5 years (Grigg-Damberger et al., 2007). From the age of 5 to 6 years, the architecture of sleep becomes progressively closer to that of young adults and sleep stages (REM and NREM) become well established (Grigg-Damberger et al., 2007; Ohayon et al., 2009) and protects novel representations against retroactive interference (Diekelmann et al., 2011). Finally, many studies have highlighted a relation between NREM stage N2 sleep spindle activity and various aspects of cognition including intellectual abilities, learning, and memory consolidation processes (for a review see Fogel and Smith, 2011). Spindles can be further differentiated between slow spindles (12–14 Hz) widely spread over frontal regions and more focal fast spindles (14–16 Hz) localized over centro-parietal regions, with these two types of spindles being subtended by different functional neuroanatomical networks (Schabus et al., 2007) and possibly associated with different cognitive processes (Clemens et al., 2007; Schabus et al., 2004, 2008).
Recent studies have suggested that sleep might be associated with intellectual and cognitive abilities in children. For instance, there is a positive correlation between sleep duration and intellectual scores in children (Geiger et al., 2010; Gruber et al., 2010). Looking at sleep features, three specific oscillatory parameters of sleep (i.e. the sleep spindles, the cyclic alternating pattern [CAP] and the SWA) have been found to follow at least partially an age-dependent developmental trajectory that may be associated with the evolution of plasticity and maturation processes (Buchmann et al., 2011). Moreover, one recent study evidenced similar age-dependent evolution between sleep SWA, cortical maturation and cognitive abilities (Kurth et al., 2012). Therefore, it might be surmised that cortical maturation as well as SWS-dependent mechanisms of brain plasticity contribute to the development of cognitive functions supporting intellectual, learning and memory consolidation abilities.

4.1.1. Sleep spindles

Sleep spindles have been proposed to be an index of cortical maturation that could indicate the severity of mental retardation and abnormal maturational processes (De Gennaro and Ferrara, 2003). Supporting this assumption, higher intelligence scores in school-aged children correlate with either the amount of sleep stage 2 (Busby and Pivik, 1983) or individual relative sigma power (Geiger et al., 2011, 2012) mainly over central and parietal areas (Geiger et al., 2012). Chatburn et al. (2013) also found a positive association between the total number of fast spindles (>13 Hz) and memory for narrative in children whereas, contrary to Geiger et al.’s (2011) study, no association was found between overall spindle activity and full-scale IQ scores (Chatburn et al., 2013). Additionally, negative associations between sleep spindle frequency and IQ test performance have been consistently found in children’s literature (Geiger et al., 2011; Gruber et al., 2013; Chatburn et al., 2013), suggesting that higher spindle frequency is associated with poorer information processing, while lower frequency would be associated with better processing. These latter findings are in contradiction with adult findings in whom increased spindle frequency was associated with better cognitive functioning (Bodizs et al., 2005; Brière et al., 2000; Fogel et al., 2007; Gaillard and Blois, 1981; Nader and Smith, 2001; Schabus et al., 2006).

Sleep spindles also develop with age. There is a gradual and moderate evolution at centro-parietal locations from 2 to 25 years, whereas frontal spindles mature with a sudden increase of frequency during puberty (Nagata et al., 1996; Shimohirotta et al., 1999). Spindle length and density follow an age-dependent maturation curve (Scholle et al., 2007) predominating around 8 to 14 years over frontal regions (Nagata et al., 1996; Shibagaki et al., 1982). These modifications are likely to reflect developmental changes in thalamo-cortical structures involved in the generation of sleep spindles (De Gennaro and Ferrara, 2003; Shibagaki et al., 1982). In line with this assumption, increased slow sigma power (11–12 Hz) and spindle activity in dyslexic children was proposed to reflect both the enhancement of cortico-cortical coupling and an over-activation in thalamo-cortical and hippocampo-cortical circuits recruited to transfer information between cortical posterior and anterior areas (Bruni et al., 2009a). In these dyslexic children, the information to be read would be transferred from a disrupted posterior system to an ancillary anterior frontal system, ultimately allowing them to decode words (Bruni et al., 2009a), but slowly and not automatically (Shaywitz and Shaywitz, 2008).

Overall, children studies suggest that reduced spindle frequency might be associated with better cognitive abilities (Gruber et al., 2013; Geiger et al., 2011; Chatburn et al., 2013) whereas higher spindle frequency would be associated with cognitive difficulties (Bruni et al., 2009a). These observations are at odds with adult studies showing that increased spindle frequency is associated with better cognitive functioning (Bodizs et al., 2005; Brière et al., 2000; Fogel et al., 2007; Gaillard and Blois, 1981; Nader and Smith, 2001; Schabus et al., 2006), and studies having investigated mainly sigma power or amount of sleep stage 2 in children. Further research is needed to
clarify the relationships between sleep spindle frequency, maturation and cognitive abilities, and whether the age-related increase in sleep spindle frequency may be associated with better cognitive abilities.

4.1.2. Cyclic alternating patterns (CAPs)

The cycling alternating pattern (CAP) is an endogenous rhythm present in NREM sleep that exhibits dramatic changes with age and allows the quantification of sleep stability (Terzano and Parrino, 2000) (for a comprehensive definition and a documented developmental evolution of CAP, see Bruni et al., 2010). Subsequent analyses conducted in the same sample of dyslexic and age-matched control children than in Bruni et al.’s (2009a) study discussed above have highlighted in dyslexic children a positive correlation between verbal IQ, full-scale IQ and reading test measures and cycling alternating pattern (CAP) sleep parameters, namely the CAP rate and the A1 index (Bruni et al., 2009b). The latter reflecting synchronized EEG patterns during SWS is also known to have a clear prevalence over anterior frontal regions (Ferri et al., 2008a; Bruni et al., 2009b) argued that increased CAP rate and A1 index during SWS might be the consequence of the transfer of information between cortical-posterior and anterior areas used by dyslexic children to overcome their reading difficulties (Bruni et al., 2009b).

Likewise, a positive correlation between intellectual abilities and CAP parameters was found in children and adolescents with an Asperger’s syndrome (Bruni et al., 2007). Furthermore in adults, a positive relationship was disclosed between CAP and memory performance (Ferini-Strambi et al., 2004). Finally, relationships between CAP and sleep-dependent gains in memory have been reported (Ferri et al., 2008), with a significant increase of the slow CAP A1 component during the post-training night following practice on a motor adaptation task (Chiardi et al., 2008), as compared to a non-rotation control condition. Moreover, changes in the A1 index were positively correlated with the overnight gain in performance, suggesting that CAP A1 linked to slow synchronized oscillations reflects underlying sleep-dependent consolidation processes (Ferri et al., 2008).

4.1.3. Slow wave activity (SWA)

As discussed above, SWA plays an important role in sleep-dependent memory consolidation processes in adults. The development of SWA appears to parallel that of cortical and cognitive maturation in children. The amplitude and the slope of slow waves (Kurth et al., 2010a) as well as SWA sharply increase until the age of 6 to 8 years then start declining (Campbell and Feinberg, 2009; Feinberg and Campbell, 2012; Jenni and Carskadon, 2004; Kurth et al., 2010b) with a sudden and marked drop around 12–16 years (Feinberg and Campbell, 2012). Buchmann et al. (2011) showed that decreased SWA activity when entering adolescence is highly correlated with a decrease in the cortical maturation observed during childhood and adolescence (mostly over the medial parietal lobe and in parts of the prefrontal cortex), reflecting the characteristic synaptic pruning processes occurring at this period (Hutchenlocher, 1979; Hutchenlocher et al., 1982; Rakic et al., 1986; Zuo et al., 2005) and allowing the development of efficient cortical networks (Buchmann et al., 2011). Additionally, using high-density EEG, anatomical magnetic resonance imaging and behavioral assessments in a wide population of children and adolescents, Kurth et al. (2012) evidenced a direct relationship between sleep SWA, anatomy and skills development. Results showed that the location of maximal SWA which, according to previous results (Kurth et al., 2010b; Shaw et al., 2008), underwent a shift from posterior to anterior regions across childhood and adolescence, was associated to the maturation of cortically-related skills. Indeed, complex motor skills (assessed through sequential finger tapping and reaction time tasks) positively correlated with the age-dependent local maxima of SWA over regions where such abilities were supposed to be grounded. Interestingly, the “back to front” SWA maturation generally preceded both skill and cortical maturation by a few years (3.7 years), suggesting that SWA might, at least to some extent, contribute to skills development, and thus putatively to long-term plasticity processes during development. The fact that age-related changes are highly specific for sleep parameters as well as for brain morphology and cognitive development suggests that those parallel maturation processes are related to common underlying mechanisms. Besides, childhood features an intense learning period. During this crucial period of development, fantastic amount of plastic processes is at play allowing children to acquire, store and sort novel information according to their relevance (Brehmer et al., 2007; Li et al., 2006). In this respect, investigating the plastic processes subtending sleep-dependent memory consolidation processes in children is of crucial importance. However, notwithstanding the utmost importance of sleep for the development of cognitive and behavioral abilities, the studies considering the interactions between sleep and memory consolidation processes from a developmental perspective are surprisingly scarce, as reviewed in the next section.

4.2. Sleep-dependent consolidation of declarative memories in children

Although only few studies have investigated sleep-dependent memory consolidation processes in children, a beneficial impact of sleep on the consolidation of declarative memories has been consistently demonstrated using different learning tasks (Backhaus et al., 2007; Prehn-Kristensen et al., 2009; Wilhelm et al., 2008; Henderson et al., 2012). Using a classical word pair learning task, two studies showed that children aged 6–8 years (Wilhelm et al., 2008) and 9–12 years (Backhaus et al., 2007) exhibit better recall performance after a night of sleep than after a similar period of wakefulness, likewise in adolescents (Portkin and Bunney, 2012) and adults (e.g. see Fowler et al., 1973; Gais and Born, 2004; Gais et al., 2006; Pilhål and Born, 1997, 1999; Wilhelm et al., 2008; for reviews see also Diekelmann et al., 2009; Peigneux and Smith, 2010). Moreover, overnight recall performance was found positively correlated with the percentage of post-training NREM sleep, and negatively correlated with the percentage of REM sleep (Backhaus et al., 2007). A correlation between post-training SWS and overnight gains in performance in a picture recognition task was also found in controls but not in children with attention deficit/hyperactivity disorder (ADHD) (Prehn-Kristensen et al., 2011a). Additionally, using both a word pair verbal learning task and a 2D object location visuo-spatial learning task (“Memory” game) to compare sleep-dependent consolidation between children and adults, Wilhelm et al. (2008) found that overnight changes in performance were similar in the two tasks, but also had the same amplitude in young and adult participants. This latter effect is worth noticing considering that the amount of SWS during post-training sleep was almost twice as large in children. Given the crucial role of SWS for memory consolidation as evidenced in adult studies, it would have been conceivable that children exhibiting larger amounts of SWS during the post-training night would have obtained proportionally larger gains in performance over a night of sleep than adults. A tentative explanatory hypothesis for this lack of effect is that weaker and/or less extensive preexistent declarative knowledge in children might modify the sleep-dependent integration/consolidation of novel memories, somehow negating the potential benefit that children could have obtained compared to adults (Wilhelm et al., 2012a). In line with this proposal, rodent studies have shown that the integration of novel memories into pre-existing activated cortical schemata proceeds very rapidly (Tse et al., 2007) reflecting the influence of prior knowledge on the consolidation rate (Osada et al., 2008). At variance with the latter hypothesis, however, it was shown that children and adults similarly benefited from sleep to integrate novel non-word representations (e.g. “biscuit”) into the mental lexicon, even though pre-existent lexical knowledge into which novel non-words had to be integrated (e.g. “biscuit”) was adapted (i.e. highly familiar words) and well-balanced for each population (Henderson et al., 2012; Dumay and Gaskell, 2007). Although sleep patterns were
not recorded in those studies, it suggests that larger amounts of SWS in children than in adults do not automatically entail proportionally larger gains in performance over a night of sleep. Nevertheless, complementary studies should probe the impact of pre-existent memory representations on memory consolidation in humans. Alternative hypotheses would be (a) that the plus-value of obtaining greater amounts of SWS in children is only observable after a sufficient integration time offline, which emphasizes the necessity to conduct delayed testing in children studies and/or (b) that sleep effectively promotes the reorganization of cortical activity in children, but that memory retrieval can be operated using different cerebral strategies leading to a similar behavioral outcome, similarly to results from adult studies (Orban et al., 2006; Rauchs et al., 2008).

4.3. Sleep-dependent consolidation of procedural memories in children

Since birth, we have developed an impressive amount of fundamental abilities through the acquisition of procedural skills and habits, both in the sensorimotor verbal and non-verbal domains (Ullman, 2004). Even more than in adults, studying how and whether post-training sleep impacts on the development and consolidation of procedural skills in children is therefore crucial to understand fine and gross motor learning but also language acquisition processes during childhood. As it stands, only few experimental studies have investigated this issue. Initial studies failed to find a sleep-dependent contribution in the consolidation of procedural memories in children. Indeed, visuo-motor sequence learning was found less improved in children after post-training sleep than in wakefulness (Wilhelm et al., 2008) or even deteriorated over sleep (Fischer et al., 2007), unlike in adults in whom sleep improved sequential skill abilities. Likewise, procedural mirror tracing abilities were not more improved after sleep than wakefulness in 10–13 year old boys (Prehn-Kristensen et al., 2009), whereas consistent sleep-dependent effects have been observed in adults using the same task (Fogel et al., 2007; Plihal and Born, 1997). To explain these discrepancies, it has been hypothesized that the competition between learning-related explicit and implicit representations on sleep-dependent memory consolidation processes may be higher in children than in adults (Fischer et al., 2007; Wilhelm et al., 2008, 2012a, 2012b). According to this proposal, the larger amounts of SWA in children’s sleep might preferentially favor the strengthening of the explicit components of sensorimotor representations, which would eventually counter sleep-dependent gains in motor performance due to declarative interference (Brown and Robertson, 2007a, 2007b; Robertson, 2009). In line with this hypothesis, children gained more explicit knowledge than adults after a night of sleep following implicit learning of a repeated motor sequence (Wilhelm et al., 2013).

Alternatively, a reduced impact of post-training sleep on the consolidation of procedural memories in children might be explained considering differences between children and adults in learning curves and performance levels achieved prior to sleep. Substantiating this hypothesis, Wilhelm et al. (2012b) found comparable overnight gains in performance when children and adult populations reached similar learning levels in a sequential visuo-motor learning task. The authors surmised that in previous studies conducted in children, the learned representations of the procedural material were not sufficiently robust to counteract the competitive impact of the explicit components in the consolidation of implicit motor representations, therefore possibly flattening overnight gains in performance (Wilhelm et al., 2012a, 2012b).

Furthermore, it can be surmised that sleep-dependent reorganization of procedural learning-related cerebral activity occurs in children in a covert manner, i.e. without behaviorally observable differences in performance on the learned material. This equality in performance on the learned material with modified underlying cerebral processes would be actually subtended by the development of different behavioral strategies, as shown in rodents (Hagewoud et al., 2010). Similar covert sleep-dependent consolidation effects have been also evidenced in adults both for declarative (Gais et al., 2007; Orban et al., 2006; Rauchs et al., 2008; Sterpenich et al., 2007) and procedural (Atienza et al., 2004; Urbain et al., in press) memories. In this framework, it was found in 15-month old infants that their memory for the features of an artificial language is decreased after sleep, but that their ability to extract abstract rule-like patterns of a novel verbal material is actually enhanced (Gomez et al., 2006). This result is reminiscent of effects observed in young zebra finch birds. Indeed, even if the structure of the learned song is actually deteriorated after nocturnal sleep, the birds showing the strongest post-sleep deterioration also eventually achieve the best song learning over time on the long term (Deregnaucourt et al., 2005). These results suggest that sleep might benefit the development of procedural memories already at an early developmental stage, although in an indirect manner. Accordingly, we have found that whereas performance equally improves in 10–12 year old children after sleep or wakefulness for the learned deviation in a visuo-motor adaptation task (adapted from Huber et al., 2004), the presentation of the opposite, unlearned deviation elicits twice as large interference effects after post-training sleep than wakefulness (Urbain et al., under revision). It indicates that sleep has contributed to the consolidation and automation of the learned visuomotor adaptation skill in children in such a way that it indirectly makes the learning of a novel but related motor skill slower, due to higher proactive interference effects from the learned onto the untrained material.

As compared to other classical procedural tasks (e.g. FFT, SRTT), a peculiarity of the rotation adaptation task is that its consolidation has been strongly linked with post-training NREM sleep slow oscillations in adults (Hill et al., 2008; Huber et al., 2004) in the framework of the synaptic homeostasis theory (Tononi and Cirelli, 2003, 2006), with positive correlations between overnight gains in performance and local increases in post-training SWA (Huber et al., 2004). Considering this relationship and the presence of consistent slow wave sleep-dependent consolidation effects in declarative memory in children (Backhaus et al., 2007; Prehn-Kristensen et al., 2009; Wilhelm et al., 2008), children may actually benefit from post-training sleep only for SWS-dependent procedural memory tasks. In line with this reasoning, other procedural tasks previously studied in children and having found time- more than sleep-dependent effects actually mostly benefit from REM and/or light non-REM (stage 2) sleep in adults. For instance, post-training sleep spindle density was associated with the consolidation of motor and visuomotor learning (Fogel et al., 2007; Peters et al., 2008; Smith and MacNeill, 1994) whereas REM nocturnal sleep (Fogel et al., 2007) and diurnal stage 2 sleep were related to the development of mirror tracing abilities (Backhaus and Junghanns, 2006). Also, it should be considered that adaptive visuo-motor consolidation processes might be qualitatively different between children and adults. For instance, 9 and 12 year old children, but not 17 year old young adults exhibit delayed gains in performance at 24 h post-learning for the trained sequence in the finger tapping task (FTT), even when exposed to an intermediate (retroactive) interfering sequence (Dorferberger et al., 2007). Reduced retroactive interference effects in 9 and 12 year old children could reflect the consolidation of general motor abilities, instead of the sequential features. However, a subsequent study showed that consolidation was only effective for the trained sequence in the three age groups (Dorferberger et al., 2012), undermining this hypothesis.

Altogether, available studies conducted in healthy children populations suggest the presence of sleep-dependent memory consolidation mechanisms during the developmental phase. However, numerous questions and inconsistencies remain to be solved, considering for instance how these mechanisms support (or not) the consolidation of procedural memories. Dedicated studies are now needed combining polysomnographic recordings, assessment of memory performance at short and delayed long-term retrieval using a comprehensive array of
direct and indirect (e.g. interference effects) behavioral measures, as well as systematic comparisons between children and adults to prove or disprove the explanatory schemes discussed above. Additionally, there is a need for neurophysiological and neuroimaging studies in children, which will hopefully enlighten our understanding of the post-training neural mechanisms underlying sleep-dependent memory consolidation processes in children, to the same extent than their adult counterparts. Finally, neurophysiological data are fundamental to understand the pathophysiological underpinnings of developmental disorders associated abnormal sleep activity, cognitive disturbances and impaired sleep-dependent plasticity processes which will be discussed in the following section.

5. Pathophysiology of sleep-dependent memory consolidation processes in children

The studies developed in the previous sections have stressed the close relationships existing between the development of sleep features (e.g. spindles, CAP, SWA), brain maturation and various cognitive processes. Additionally, many studies have demonstrated a prominent impact of sleep-dependent oscillatory mechanisms on memory consolidation processes. In this respect, sleep disturbances in children with or without developmental disorders may contribute to the pathogenesis of cognitive disabilities and impaired memory consolidation in these populations. Accordingly, performance on a pictorial memory task was characterized by a slower learning curve and decreased overnight performance in 6–16 year old children with obstructive sleep apnea [OSA] resulting in highly fragmented sleep, as compared to healthy controls who have stabilized performance over sleep (Kheirandish-Gozal et al., 2010). Although this result suggests an effect of sleep perturbations on cognitive processes, the fact that performance was already compromised during the acquisition phase, together with the absence of a post-training control wake condition does not allow to conclude to a sleep-dependent impairment of memory consolidation in children with OSA.

5.1. Sleep, memory and attention deficit/hyperactivity disorder (ADHD)

At variance, relationships between sleep-dependent memory consolidation and sleep maturation have been highlighted in children suffering from an attention deficit/hyperactivity disorder (ADHD) syndrome. Whereas recognition of explicitly learned pictures was better after sleep than wakefulness in both 10–16 year old children with ADHD and matched controls, sleep-dependent gains in performance were found markedly reduced in ADHD children. Additionally, overnight gains in performance were positively correlated with post-training SWA in controls but not in children with ADHD (Prehn-Kristensen et al., 2011a). The ADHD syndrome features an atypical functioning of the prefrontal cortex and striate brain regions (Bush et al., 2005; Rubia et al., 1999; Shaw and Rabin, 2009; Zang et al., 2005) as well as of connectivity patterns between these areas (Massat et al., 2012). In this framework, it can be hypothesized that a reduced sleep-dependent enhancement of declarative memories in children with ADHD is linked to frontal dysfunctions in this specific population (Wilhelm et al., 2012a). Furthermore during sleep, the topographical distribution of SWA appears to present a maturational delay with an increase of SWA power over central regions as compared to age- and sex-matched healthy controls (Ringli et al., 2013), despite a globally similar topographic distribution (Kurth et al., 2010b). In healthy subjects, the topographical evolution of SWA is characterized by an age-dependent shift of local maxima from occipital to central areas during the transition from early to late childhood, then to frontal areas in late adolescence (Kurth et al., 2010b, 2012). In children with ADHD, local maxima of SWA located posteriorly to that of control subjects along the posterior–anterior axis can be interpreted as a delayed progression of SWA to frontal regions reflecting a neuro-maturational delay. Besides, the prefrontal cortex may contribute to a “motivational” tagging of memories (Miller, 2000). This tagging would make the memories that are the most relevant for the subject’s future a preferential target for sleep-dependent consolidation processes, as recently suggested in adults (Wilhelm et al., 2011). In this context, it was hypothesized that this prefrontal-related process might be altered in children with ADHD preventing them to create effective prospective markers, eventually leading to reduced sleep-dependent enhancement in declarative performance (Wilhelm et al., 2012a).

The consolidation of procedural memories has been also investigated in children with ADHD using an adapted version of the SRT task (Prehn-Kristensen et al., 2011b). Interestingly, children with ADHD obtained a better performance after a night of sleep than after a similar period of wakefulness, whereas sleep was not more beneficial than wake in healthy control children, according to previous studies (Fischer et al., 2007; Prehn-Kristensen et al., 2009; Wilhelm et al., 2008). More precisely, performance in children with ADHD was deteriorated after wakefulness but kept at the same level than controls after sleep. Nonetheless, overnight gains in performance were correlated with the amount of SWS and with REM sleep density in ADHD children only, suggesting that sleep plays an active role in the consolidation of procedural memory. Likewise, adolescents having presented iron deficiency anemia in infancy affecting the dopaminergic neurotransmission system have been found to improve performance on the finger-tapping task after nocturnal sleep, which was not the case for the control population (Algarin et al., in preparation). In children with ADHD, it has been suggested that a benefit of post-learning sleep for the consolidation of procedural memory might be associated with a weaker capacity to benefit from sleep for the consolidation of declarative/explicit representations of motor memories (Prehn-Kristensen et al., 2011a). A reduced weight of explicit representations would therefore diminish the impact of the competitive interaction between explicit and implicit components of motor memories, eventually resulting in offline gains in performance for procedural memories unlike in healthy controls (Prehn-Kristensen et al., 2011b; Wilhelm et al., 2012a). It has been generally assumed that children with ADHD experience problems in initiating and maintaining sleep (Cortese et al., 2009; Konofal et al., 2010; Wiebe et al., 2013) with a reduced sleep duration and an increased rate of stage shifts suggesting a hypoarousal state (Miano et al., 2006). Therefore, sleep difficulties in the ADHD have been mostly viewed as an epiphenomenon of an underlying maturational disorder. The studies discussed above suggest that the borders between cortical and sleep maturation are blurred in ADHD, and that further investigations are needed to better understand how sleep disturbances are contributing factors of their cognitive deficits.

5.2. Pathophysiology of sleep-dependent memory consolidation in epilepsy

Pathophysiological sleep-dependent memory consolidation processes have been recently evidenced in some types of childhood epilepsies. It has been hypothesized that chronically abnormal sleep activity might be a causal factor of cognitive and learning disabilities in epileptic children (Billard et al., 2009; Chan et al., 2011; Van Bogaert et al., 2011), besides the possible contribution of ongoing seizures and/or antiepileptic drug (AED) treatments (Berg et al., 2008; Fastenau et al., 2009). In particular, the impact of interictal (infra-clinical) epileptic activity (IEA) on cognition is well recognized in the epilepsy with continuous spike and waves during slow wave sleep (CSWS) (Tassinari et al., 2009). In particular, the impact of interictal (infra-clinical) epileptic activity (IEA) on cognition is well recognized in the epilepsy with continuous spike and waves during slow wave sleep (CSWS) (Tassinari et al., 2009). In particular, the impact of interictal (infra-clinical) epileptic activity (IEA) on cognition is well recognized in the epilepsy with continuous spike and waves during slow wave sleep (CSWS) (Tassinari et al., 2009). In particular, the impact of interictal (infra-clinical) epileptic activity (IEA) on cognition is well recognized in the epilepsy with continuous spike and waves during slow wave sleep (CSWS) (Tassinari et al., 2009). In particular, the impact of interictal (infra-clinical) epileptic activity (IEA) on cognition is well recognized in the epilepsy with continuous spike and waves during slow wave sleep (CSWS) (Tassinari et al., 2009). In particular, the impact of interictal (infra-clinical) epileptic activity (IEA) on cognition is well recognized in the epilepsy with continuous spike and waves during slow wave sleep (CSWS) (Tassinari et al., 2009). In particular, the impact of interictal (infra-clinical) epileptic activity (IEA) on cognition is well recognized in the epilepsy with continuous spike and waves during slow wave sleep (CSWS) (Tassinari et al., 2009).
observed in children with epilepsy. Further investigations are needed to investigate this promising and exciting avenue of research.

6. Conclusions

Over the past decade, accumulated evidence has shown that sleep contributes to the consolidation of declarative memories in children. How and whether sleep helps in consolidating verbal and non-verbal procedural skills in this population remains a matter of debate and deserves further investigations. Dedicated studies combining comprehensive behavioral measures, neurophysiological and/or neuroimaging recordings in healthy and pathological populations are crucially needed to unravel the mechanisms subverting the evolution of sleep-dependent memory consolidation processes during childhood. Especially, we believe that neurophysiological and neuroimaging investigations may contribute to enlighten the pathophysiological associations linking abnormal sleep patterns, cognitive disturbances and impaired sleep-dependent plasticity processes throughout the developmental phase. These investigations should be conducted in parallel with the study of pathological conditions in which children present abnormal sleep patterns and cognitive deficits, such as, for a few instances, ADHD, specific language impairments and epileptic syndromes. In this respect, comparing the development of sleep-dependent plasticity markers (i.e. spindles, CAP, SWA) in children with or without cognitive disorders, and how this evolution interacts with cognitive functioning and/or cortical maturation, constitutes a promising field of research to understand the pathophysiological conditions subverting the long-term disruption of cerebral plasticity processes involved in memory consolidation during sleep.

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References


Stephani and Carlsson, 2006). Notwithstanding, an association was suggested between the frequency and diffusion of IEA during slow-wave sleep and the severity of behavioral and cognitive deficits (for a review see Van Bogaert et al., 2011). Focusing on sleep-dependent memory consolidation processes, we have investigated the specific impact of IEA during post-training sleep on the consolidation of declarative memories in 4 cases of idiopathic focal epilepsy and a population of age-matched control children (Urbain et al., 2011). In line with prior studies (Backhaus et al., 2007; Prenk-Kristensen et al., 2009, 2011a; Wilhelm et al., 2008), the recall of learned word pairs was higher after sleep than after wakefulness in the control population. Although the children with idiopathic focal epilepsy reached same levels of performance than controls at the end of the learning phase, their performance was dramatically deteriorated after a night of sleep, suggesting impaired sleep-dependent memory consolidation. This result was in line with studies conducted in adults and children with epilepsy, demonstrating accelerated long term forgetting (ALF) effects over days despite normal levels of learning and retention on the short term (Blake et al., 2000; Butler and Zeman, 2008; Cronel-Ohayon et al., 2006; Gallassi et al., 2011; but see McGibbon and Jansari, 2013). To test the hypothesis that IEA during post-training sleep plays a potentially causal role in memory consolidation disturbances, the experiment was repeated in 2 children with CSWS after one month of hydrocortisone treatment that aimed at reducing IEA. Sleep EEG was completely normalized after treatment in one child, and partially improved in the other. Noticeably, overnight gain in performance was back to the level of healthy controls only in the child totally devoid of sleep-related IEA, suggesting that interictal epileptic discharges indeed disrupt sleep-dependent memory consolidation processes (Urbain et al., 2011).

Children with CSWS present an abnormal metabolic pattern for glucose, characterized by focal hypermetabolism at the epileptic focus and hypometabolism at distant connected areas, which normalizes in parallel with EEG abnormalities (De Tiège et al., 2008, 2009). This pattern suggests that IEA-induced cognitive deficits are related not only to the functional repercussions of epileptic activity at the site of the epileptic focus, but also to the remote functional inhibition of brain areas connected to the epileptic focus. Hypermetabolic areas are mainly located over centro-parietal region, whereas hypometabolic patterns encompass the frontal lobes. This metabolic imbalance may impair the sleep-dependent reorganization of cerebral activity subtending memory consolidation processes (Gais et al., 2007; Takashima et al., 2006) in the framework of the model of the hippocampo-neocortical dialogue (Born and Wilhelm, 2012), and have an impact on cognitive performances in epileptic children (De Tiège et al., 2008, 2009).

Finally, a recent study (Bolsterli et al., 2011) has substantiated the hypothesis that pathophysiological sleep-related conditions in children with idiopathic focal epilepsy might contribute to the impairment of the neurophysiological mechanisms subtending memory consolidation processes. This study was conducted in the framework of the Synaptic Homeostasis Hypothesis proposing that sleep-dependent memory consolidation results from use-dependent synaptic downscaling processes triggered by NREM slow sleep oscillations, eventually increasing the signal-to-noise ratio of the newly encoded information (Tononi and Cirelli, 2003, 2006). To test the impact of IEA on synaptic downscaling processes in 9 children with CSWS (3–11 year old) as compared to controls, they analyzed the time course of the slope of slow waves (0.5–2 Hz). In line with previous studies (Kurth et al., 2010a; Riedner et al., 2007), healthy controls exhibited an overnight decrease in the slope of slow waves. At variance, SWA during NREM sleep and the slope of slow waves remained unchanged from the first to the last hour of sleep in children with CSWS (Bolsterli et al., 2011), indicating a disruption of synaptic downscaling processes in epileptic children.

In this respect, the studies described in this section suggest a reduced plasticity during sleep that may impact on sleep-dependent consolidation processes and contribute to the cognitive and learning deficits


