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Sleep in children triggers rapid reorganization of memory-related brain processes

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ABSTRACT

Behavioral evidence shows that sleep is crucial for the consolidation of declarative memories in children as in adults. However, the underlying cerebral mechanisms remain virtually unexplored. Using magnetoencephalography, we investigated in children the impact of sleep (90-minute nap) on the neurophysiological processes underlying the creation and consolidation of novel associations between unknown objects and their functions. Learning-dependent changes in brain activity were observed within hippocampal and parahippocampal regions, followed by sleep-dependent changes in the prefrontal cortex, whereas no equivalent change was observed after a similar period of wakeful rest. Hence, our results show that a 90-minute daytime nap after learning is sufficient to trigger the reorganization of memory-related brain activity toward prefrontal areas, where it incorporates into pre-existing semantic knowledge. This functional reorganization process in children is similar to that observed in adults but occurs at a much faster rate, which may contribute to the development of the outstanding learning skills that characterize childhood.

Introduction

Children learn at an outstanding pace during their development. Especially at school age, they quickly consolidate novel verbal material, a process that requires the associative binding of arbitrarily related information (Cohen et al., 1997; Squire and Knowlton, 2000). Like in healthy young adults (Wilhelm et al., 2013), post-learning sleep appears to further benefit memory consolidation for verbal and non-verbal declarative memories in children (Huber and Born, 2014; Urbain et al., 2013b; Wilhelm et al., 2012a). However, the neurophysiological underpinnings of sleep-dependent memory consolidation processes in children remain virtually unexplored.

According to system consolidation theories, recently learned information is quickly stored and temporarily held in hippocampal regions, then gradually transferred toward neocortical long-term memory stores (Marr, 1971; McClelland et al., 1995). Buzsaki (1996) additionally proposed that memory consolidation takes place across multiple iterations of the sleep–wake cycle, hippocampal information being progressively transferred toward neocortical stores during slow wave sleep (SWS). Interactions between high-frequency bursts of neuronal activity in the hippocampus (sharp wave ripples) and thalamo-cortical spindles, both triggered during the depolarizing ("up") phase of the slow oscillations, support information transfer during SWS (Diekelmann and Born, 2010). Neuroimaging PET and fMRI studies conducted in young adults have provided support for a role of sleep in system consolidation. For instance, activity in hippocampal areas during learning to navigate a novel environment or learning to associate pairs of cards is re-expressed during SWS on the subsequent night, spontaneously (Peigneux et al., 2004) or upon cueing (Rasch et al., 2007). Additionally, fMRI studies evidenced a sleep-dependent hippocampo-cortical or subcortical reorganization of learning-related neural activity in adults (Orban et al., 2006; Rauchs et al., 2008; Urbain et al., 2013c), even in the absence of overt, observable changes in behavioral performance. In particular, successful recall of new verbal or nonverbal representations, which is associated immediately after learning with hippocampal and parahippocampal activities, was shown associated several days to months later with activity in medial prefrontal neocortical areas, but only in participants allowed to sleep after learning; especially, sleep-

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dependent effects were found in the left medial prefrontal (mPFC, Takashima et al., 2006) and the inferior fontal (IFG; Takashima et al., 2009) cortices. Finally, triggering slow oscillations during post-training SWS strengthens the consolidation of novel declarative memories (Marshall and Born, 2011), and cueing memories during SWS protects novel representations against retroactive interference (Diekelmann et al., 2011).

From a developmental perspective, increasing behavioral evidence suggests a better consolidation of declarative memories over sleep than wakefulness in children (Ashworth et al., 2014; Backhaus et al., 2008; Galer et al., 2015; Giganti et al., 2014; Urbain et al., 2011; Wilhelm et al., 2008; Williams and Horst, 2014). It is worth noticing that most of these behavioral studies used similar declarative memory tasks (e.g. learning of word pairs). At the neurophysiological level, brain imaging studies investigating the role of sleep for memory in children are surprisingly scarce, especially considering the utmost importance of memory consolidation processes for the development of cognitive and behavioral abilities. Also, children exhibit distinctly greater amounts of SWS than adults (Kurth et al., 2010a; Ohayon et al., 2004), which might promote memory and brain plasticity processes. Accordingly, slow-wave activity locally increases in learning-related areas during post-training sleep in young children, even more than in older children and adults, suggesting developmental changes in experience-dependent plasticity (Wilhelm et al., 2014). Also, children gain more explicit representations for implicitly learned sequences than adults after sleep (Wilhelm et al., 2013). Such memory advantage associated with higher SWS and stronger hippocampal activation at explicit knowledge retrieval has been tentatively ascribed to an enhanced reprocessing of hippocampal memory representations during SWS in children (Wilhelm et al., 2013). However, no study to date has investigated the impact of sleep on the brain processes underlying the consolidation of new declarative memories in children, in spite of the close links between the development of sleep features (e.g. spindles or slow wave activity), brain maturation and cognitive processes (Huber and Born, 2014; Kurth et al., 2012). Furthermore, pathophysiological plasticity processes might impair sleep-dependent consolidation of declarative memory in children with developmental disorders or epilepsy (Galer et al., 2015; Urbain et al., 2013b).

In the present study we explored using magnetoencephalography (MEG) the specific impact of sleep on the neurophysiological processes subtending the learning and ongoing consolidation of newly formed associations between unknown objects and their functions, i.e. a core mechanism in the development of conceptual, cognitive and declarative knowledge in children. To do so, we characterized learning-related changes in brain activity in 21 healthy children (mean age 10 years) during three picture-viewing and definition sessions (Fig. 1). First, evoked magnetic field (EMFs) responses were recorded and compared between sessions, i.e. at baseline before [Session 1] learning the non-objects' functions and at retrieval immediately after learning [Session 2]. In between the immediate [Session 2] and delayed [Session 3] retrieval sessions, half of the children were allowed a 90-minute nap (Sleep condition) while the other half had a similar period of wakeful rest (Wake condition). Direct comparisons between EMFs at delayed retrieval Session 3 in the Sleep vs. Wake condition aimed at investigating the specific impact of sleep on the newly learned representations and the related consolidation mechanisms. Previous fMRI studies conducted in adults have shown sleep-related changes in memory-related brain activity, in hippocampal then neocortical locations, in the absence of overt behavioral changes (e.g. Gais et al., 2007; Rauchs et al., 2008). Likewise in the present study, we expected that the acquisition and then the sleep-dependent consolidation of novel associations (i.e. object-function) would express through local changes in brain activity, with or without detectable behavioral modifications in memory retrieval. In line with system consolidation theories, immediate retrieval should mostly associate with brain activity in hippocampus-related areas, an activity that may progressively transfer with sleep toward neocortical areas subtending the long-term storage of verbal representations.

Materials and methods

Participants

Twenty-six healthy children and their parents gave written informed consent to participate in this experiment approved by the Biomedical Ethics Committee of the Erasme Hospital — Université Libre de Bruxelles (ULB). All children were native French speakers with no known learning, language or neurological problem. Five children had to be excluded due to poor magnetoencephalographic (MEG) signal quality or EMG/EOG artifacts contamination (see MEG data analysis below). Consequently, the final sample was composed of twenty-one healthy children (10 boys; mean age: 10.1 years; range, 8.0–12.5 years). Participants were randomly assigned either to a nap Q7 (*Sleep*, 11 children, 5 males) or a rest (*Wake*, 10 children, 5 males)

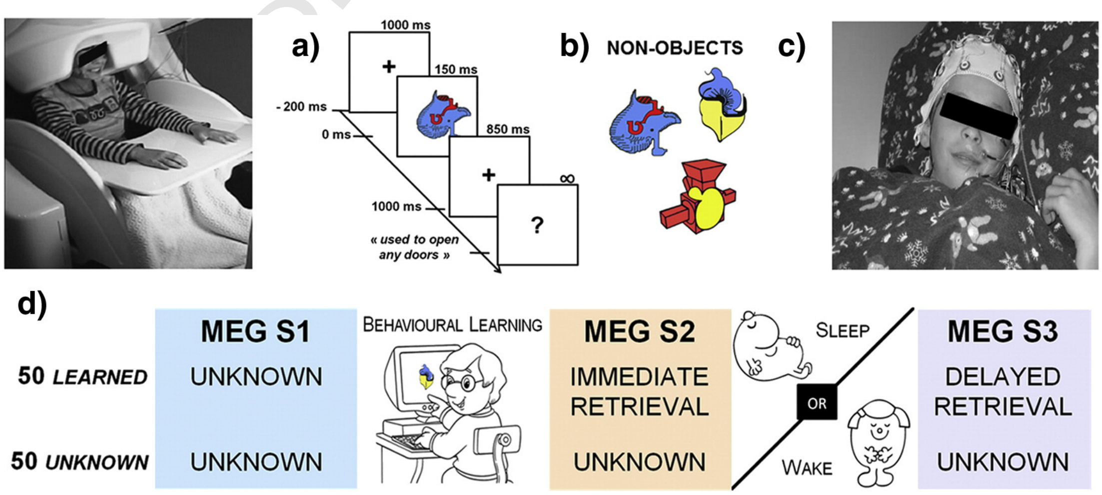

Fig. 1. Experimental task and protocol. (a) Picture definition task: at each MEG session, children were asked to provide the definition of the non-object presented on the screen or to signal if the object was unknown. Responses had to be given after the appearance of the question mark (1 s after stimulus onset). (b) Sample illustrations of the 100 non-objects (50 *learned* or to-be-*learned* non-objects and 50 *unknown* non-objects) used in this study. (c) Sleep EEG recording took place between the immediate (Session 2 [S2]) and delayed (Session 3 [S3]) MEG retrieval sessions in the *Sleep* group. (d) Experimental protocol: evoked magnetic fields during processing of learned and unknown objects were recorded during MEG Session 1 (pre-learning S1), Session 2 (immediate post-learning S2) and Session 3 (delayed retrieval after either a 90 min nap or an equivalent period of wake rest, S3).

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