

The effect of Sleep-Disorder Breathing on declarative and non-declarative memory processes in children and adults

Eszter, Csábi
Ph.D. Thesis

Department of Cognitive and Neuropsychology
Institute of Psychology
University of Szeged

Supervisor: Dezső, NÉMETH PhD.

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Summary

Numerous studies with healthy participants indicate that sleep contributes to the consolidation of memory traces by enhancing neuronal plasticity. This sleep-related reconsolidation mechanism is required for the memory representations to become more resistant to interference and being forgotten. However, remarkably little is known of the effect of sleep disorder on different memory processes. For this, here we present four studies to investigate the effect of sleep disorder on different memory processes and consolidation in children and adults. Moreover, our fifth study examined the effect of short-term positive airway pressure treatment in adult patients with obstructive sleep apnea (OSA). In **Study I**, we investigated the effect of disrupted sleep on declarative and non-declarative forms of learning in children with sleep-disordered breathing (SDB). In **Study II**, we examined the consolidation of these memory processes in children with SDB. In case of online learning, our results showed that children with SDB exhibited generally weaker declarative memory performance while the online non-declarative learning was preserved. Regarding the offline changes, we found intact consolidation in the case of declarative memory as well as sequence-specific and general skill aspects of non-declarative memory in SDB. In **Study III**, we investigated the more attention-demanding working memory performance and less attention-demanding non-declarative learning in adult OSA patients. In **Study IV**, we tested the consolidation of general skill and sequence-specific aspects of non-declarative memory. In the case of online learning, we observed that OSA patients showed general skill learning and sequence-specific learning similar to that of controls. In contrast, the working memory performance was impaired in the OSA group. In the case of the consolidation on non-declarative learning we revealed differences in offline changes of general skill learning between OSA patients and controls. The control group showed offline improvement from evening to morning, thus they became faster in the morning after the offline period, while the OSA group did not. In contrast, we failed to find differences in the offline changes of sequence-specific knowledge between the groups. Finally, in **Study V**, we examined the effectiveness of positive airway pressure treatment after two and half month. We revealed significant improvement in the respiratory functions during sleep which led to improvement in sleep pattern and reduced sleepiness. In the case of cognitive functions we observed significant improvement in complex working memory, short- and long-term verbal memory and short-term visual memory. In contrast, the OSA patients demonstrated significant impairment in long-term visual memory. In case of anxiety, we found significant improvement in state anxiety level and trend in trait anxiety which was correlated with

hypoxic events during sleep. Furthermore, we found a positive correlation between slow wave sleep and executive functions. The respiratory functions and hypoxic events during sleep associated negatively with executive functions and explicit memory.

Our results can give us a deeper insight into the effect of sleep on the developing brain and memory functions and how changes the relationship between sleep and memory from childhood to adulthood. Moreover, these results can help us develop more sophisticated diagnostic tools, neuropsychological profile and more effective rehabilitation programs. Furthermore, our results complement sleep-dependent memory consolidation models well and draw attention the fact that sleep might have less influence on the structures related to implicit processes.

Introduction

Currently, there is a growing interest within cognitive neuroscience and neuropsychology to understand the underlying mechanisms of memory consolidation; namely, how newly acquired and initially labile memory representations become stable and resistant to interference and forgetting (Diekelman & Born, 2010). Previous studies with healthy participants indicate that sleep contributes to the consolidation of memory traces by enhancing neuronal plasticity which leads to the memory representation being more resistant to interference and forgetting (Diekelman et al., 2009). Remarkably little is known of the effect of sleep disorder on different memory processes and consolidation. Moreover, the effects of sleep disorder on different memory functions controversial both in children and adults. Thus, the lack of empirical studies and the controversial results motivated our experiments.

Aim of the studies

Here we present four studies investigating the effect of sleep disorder on different memory processes in childhood and adulthood. In **Study I**, we examined the effect of sleep disorder on different memory systems (namely declarative and non-declarative memory) by comparing children with sleep-disordered breathing and healthy control participants. In **Study II**, we investigated the effect of sleep disorder on the consolidation of different memory systems in children with SDB compared to healthy control subjects. In **Study III**, we compared implicit sequence learning and working memory performance in adult patients with OSA and healthy control participants to examine the effect of sleep disorder on less and more attention demanding memory processes. In **Study IV**, we compared the consolidation of implicit sequence learning in adult OSA patients and healthy control subjects to investigate the influence of sleep disorder on the offline consolidation of implicit sequence learning. In the last study (**Study V**), we evaluated the beneficial effect short-term continuous positive airway pressure (PAP) treatment on respiratory events during sleep, cognitive functions and anxiety in adult OSA patients.

Study I.

Material and methods

We compared 10 children with SDB (average age: 8.8 years, SD: 1.68; average education: 2.1 years, SD: 1.66; 5 females/ 5males) with 10 healthy control participants (average age: 9.3 years, SD: 2.45; average education: 3.3 years, SD: 2.54; 7 females/ 3 males)

matched by age and education. We used Alternating Serial Reaction Time (ASRT) task to measure non-declarative/ implicit sequence learning. In this task a dog's head appeared in one of the four empty circles on the screen and the participants had to press the corresponding button as quickly and as correctly as possible (Howard & Howard, 1997). We used War of the Ghost Test to measure declarative memory performance. In this test children are required to listen to a short story and then recall it immediately (Bartlett, 1932). We administered the "The War of the Ghosts" and ASRT task in one session between 7 PM and 9 PM both in SDB and control groups.

Results

The SDB group demonstrated significant lower declarative memory performance compared to control group while the non-declarative memory performance was preserved. We failed to find differences between the groups neither general skill nor sequence-specific learning.

Study II.

Material and methods

We compared 16 children with SDB (average age: 8.56 years, SD: 2.31; 6 females/ 10 males) and 16 healthy control participants (average age: 8.75 years, SD: 1.44; 8 females/ 8 males) matched by age, gender and parental education. We used the same ASRT task to measure non-declarative learning and War of the Ghost Test to measure declarative learning as in **Study I**. There were two sessions in the experiment: the Learning Phase (Session 1) was at 7 PM to 9 PM prior to sleep and the Testing Phase (Session 2) was at 7 AM to 9 AM after sleep thus, the average interval between the Learning and Testing Phase was 12 hours.

Results

We found intact consolidation in the case of declarative memory as well as sequence-specific and general skill aspects of non-declarative memory in SDB however, the SDB group demonstrated generally lower declarative memory performance compared to control group in both sessions.

Study III.

Material and methods

We compared twenty previously untreated Obstructive Sleep Apnea (OSA) patients (average age: 52.70, SD: 9.60; average education: 11.95, SD: 2.62, 3 female/17 male) with 20 healthy control subjects (average age: 52.40, SD: 15.04, average education: 12.65, SD: 3.56, 5 female/15 male) matched by age, education and gender. The mean Apnea-Hypopnea Index (AHI) was 50.76 events/hour, SD: 22.20 (Range: 21.10-117.30). We used the same ASRT task to as in **Study I and II**. We used Listening Span Task to measure working memory performance (Janacek et al., 2009). We administered the Listening Span Task and ASRT task in one session between 6 PM to 9 PM both in OSA and control groups.

Results

We revealed that the less attention-demanding general skill- and sequence-specific learning similar to that of controls. In contrast, the more attention-demanding working memory performance was impaired in the OSA group.

Study IV.

Material and methods

We compared seventeen newly diagnosed and untreated OSA patients (average age: 52.41 years, SD: 9.67; 2 females/15 males) with 17 healthy control subjects (average age: 54.24 years, SD: 7.29) matched by age and working memory performance. We used the same ASRT task as in the previous experiments. There were two sessions in the experiment: a Learning Phase (Session 1) and a Testing Phase (Session 2) for both the OSA and the healthy control group. The sequence learning performance was assessed between 7 PM to 8 PM prior to sleep (Learning Phase) and between 7 AM to 8 AM after sleep (Testing Phase), thus the average interval between the Learning and Testing Phase was 12 hours.

Results

We revealed differences in offline changes of general skill between OSA patients and controls. The control group showed offline improvement from evening to morning, thus they became faster in the morning after the offline period, while the OSA group did not. In contrast, we failed to find differences in the offline changes of sequence-specific knowledge between the groups.

Study V.

Material and methods

Twenty-four newly diagnosed and untreated patients with OSA participated in the experiment (average age: 53.21 years, SD: 12.11; average education: 12.17 years, SD: 2.20; 1 females/15 males). The mean AHI was 54.07 event/hour (SD: 23.26). We measured short- and long-term verbal- and visual- memory, complex working memory, executive functions, anxiety, the sleep structure and sleepiness.

There were 3 Sessions in the experiment: diagnostic night (Session 1); titration night (Session 2) and after 2 and half month of CPAP/BiPAP treatment (Session 3). In the first two Sessions, we used polysomnography to measure sleep stages and respiratory functions during sleep. In Session 3 we used polygraph to analyze the abnormal breathing during sleep. There were two neuropsychological assessments: in Session 1 and Session 3. The data collection was assessed between 7 PM to 8 PM in both cases. After the two and half month therapy, the average usage of PAP devices was 370 hour.

Results

After treatment, we revealed significant improvement in the respiratory functions during sleep which led to improvement in sleep structure and reduced sleepiness. In the case of cognitive functions we observed significant improvement in complex working memory, short- and long-term verbal memory and short-term visual memory. In contrast, the OSA patients demonstrated significant impairment in long-term visual memory. A case of anxiety, we found significant improvement in state anxiety level and trend in trait anxiety which was correlated with hypoxic events during sleep thus, the therapy has positive effect on anxiety. We found moderate positive correlation between slow wave sleep and executive functions and spindle activity in NREM 3 and NREM 4 also showed moderate positive correlations with complex working memory performance. In the case of respiratory functions during sleep, executive functions were correlated negatively with hypoxic events during sleep and sleepiness. Furthermore, immediate and delayed story recall was moderately associated with hypoxic events during sleep.

Discussion

In **Study I** and **Study II**, we investigated the effect of sleep disruption on declarative and two aspects of non-declarative memory functions and the consolidation of these different memory processes in children with SDB compared to healthy control subjects. In the case of

learning phase, our results showed that children with SDB exhibited generally weaker declarative memory performance while the non-declarative performance in the learning phase was preserved. Regarding the offline changes, we found intact consolidation in the case of declarative memory as well as sequence-specific and general skill aspects of non-declarative memory in SDB.

Our results on declarative memory performance in the learning phase are in line with previous studies that found weaker declarative memory performance in the SDB group (e. g. Gottlieb et al., 2004). The mechanism causing these memory deficits has not been fully explored. Results from previous studies supposed that sleep fragmentation and intermittent hypoxia could have negative influence on the developing brain resulting structural changes in the neural circuits, particularly in the hippocampus and frontal lobe (e. g. Halbower et al., 2006). In the case of the offline changes of declarative memory, there was a general group difference in the overall performance, but both groups showed intact overnight consolidation. This result contradicts the findings of Kheriandish-Gozal et al. (2010) who observed decreased consolidation of declarative memory in children with obstructive sleep apnea. The difference between the two studies might be explained by the type of materials to be remembered (verbal vs. non-verbal) or other task characteristics (e.g. number of repetitions). Another possible explanation might be that the SDB group in our study demonstrated floor effect with no room to forget or improve in the offline period. Furthermore, we cannot exclude the explanation that the lower performance was caused by fatigue and lower arousal because declarative memory depends on attentional resources to a higher extent than non-declarative learning.

In the case of non-declarative learning, only a few studies have examined the implicit sequence learning in children with SDB. Our results are in line with previous work that revealed similar performance in learning function between children with obstructive sleep apnea and healthy controls (Halbower et al., 2006). Moreover, these findings are similar to those of previous studies, which found no sleep-related improvement in non-declarative memory processes in healthy children (e. g. Prehn-Kristensen et al., 2009). Based on these and our results, we can suggest that permanent sleep disturbances have less influence on sequence-specific learning in childhood. In addition, our results consistent with sleep deprivation studies in adults, which demonstrated intact non-declarative learning (Serial Reaction Time; SRT) (e.g. Van der Werf et al., 2011). To our knowledge, the consolidation on non-declarative memory has not been tested in children with SDB yet. There are few studies investigating non-declarative memory consolidation in adult with OSA. For example,

Djonlagic et al. (2012) also examined adult OSA population and revealed that OSA and control groups showed almost identical performance in the initial training in the evening on a sequence learning task, but the control group exhibited significantly more overnight improvement. The authors suggest that this weaker offline performance was caused by sleep fragmentation in OSA. These differences between adults and children highlight the importance of developmental factors in the consolidation of non-declarative memory. Sleep disorder breathing might affect the underlying neural network differently in childhood compared to adulthood.

In **Study III** and **Study IV**, we examined the effect of sleep disturbances on non-declarative/implicit sequence learning and working memory processes and the consolidation of non-declarative/implicit sequence learning in patients with obstructive sleep apnea compared to healthy controls. In the case of the learning phase, we observed that OSA patients showed general skill learning and sequence-specific learning similar to that of controls. In contrast, the working memory performance was impaired in the OSA group. In the case of the consolidation of non-declarative learning we revealed differences in offline changes of general skill between OSA patients and controls. The control group showed offline improvement from evening to morning, thus they became faster in the morning after the offline period, while the OSA group did not. In contrast, we failed to find differences in the offline changes of sequence-specific knowledge between the groups. Thus, we found dissociation in these two aspects of non-declarative memory consolidation.

Our results on working memory performance are similar to those of earlier studies showing impaired working memory in the OSA group. The cause of this low working memory performance can be linked to the dysfunction of the frontal lobe (Cosentino et al., 2008). In the case of non-declarative learning, we revealed intact learning curves which are in line with previous studies investigating non-declarative learning in OSA patients (e. g. Archbold et al., 2009). Our findings are similar to those of previous sleep-deprivation studies, which found intact non-declarative performance in spite of sleep disruption (Van der Werf et al., 2011). In another type of non-declarative memory, Naegele et al. (1995) found significant but weaker learning in sensorimotor adaptation task in OSA patients than in the control group. The authors suggest that patients with OSA have difficulties creating new sensorimotor coordination.

In the overnight consolidation of non-declarative memory, we found weaker performance on general skill learning in OSA patients compared to the controls who demonstrated offline general skill improvement after the 12-hour delay period. A recent

sequence learning study by Djonlagic et al. (2012) also demonstrated that OSA patients and controls displayed almost identical performance during the initial learning in the evening, but the control group exhibited significantly more overnight improvement. The authors concluded that this weaker offline performance was caused by sleep fragmentation in OSA. In case of the offline changes of sequence-specific learning, we found similar performance between the OSA and control groups. It suggests that sleep might have less influence on this specific aspect of non-declarative learning.

In **Study V**, we investigated the beneficial effect of two and half month of continuous positive airway pressure treatment on respiratory events during sleep, cognitive functions and anxiety in adult OSA patients. After treatment, we revealed significant improvement in the respiratory functions during sleep which led to improvement in sleep structure and reduced sleepiness. In the case of cognitive functions, we observed significant improvement in complex working memory, short- and long-term verbal memory and short-term visual memory. In contrast, the OSA patients demonstrated significant impairment in long-term visual memory. In the case of anxiety, we found significant improvement in state anxiety level and trend in trait anxiety which was correlated with AHI, thus the therapy has positive effect on anxiety. We found moderate positive correlation between slow wave sleep and executive functions and spindle activity in NREM 3 and NREM 4 also showed moderate positive correlations with complex working memory performance. In the case of respiratory functions during sleep, executive functions were correlated negatively with RDI, AHI and sleepiness. Furthermore, immediate and delayed story recall was moderately associated with RDI and immediate story recall also showed moderate correlation with RDI.

Our results on respiratory functions during sleep and sleep characteristics are in line with previous studies which observed improvement in abnormal breathing during sleep which led to increased slow wave sleep and REM sleep and decreased light sleep stages (e. g. Heinzer et al., 2001). Our findings of working memory performance are similar to the findings of Felver-Gant et al. (2007), however they found no improvement on verbal episodic memory. In contrast, Thomas et al. (2005) did not observed improvement in working memory performance after 2 months of PAP treatment suggesting that OSA cause irreversible damages on dorsolateral prefrontal activity that the underlying mechanism of working memory.

Similar to our results, previous studies revealed improvement in verbal episodic memory after short- and long-term PAP treatment in OSA patients. Nevertheless, these studies failed to found impairment in long-term visual memory performance (e.g. Borak et al.,

1996). The possible explanation might be that these studies examined mild OSA patients after 3 months treatment. In our study, we measured moderate to severe OSA patients after 2 and half month therapy.

In the case of anxiety, our results are in line with previous studies which observed improvement in anxiety level after short-term CPAP treatment (Jokic et al., 1998). In contrast, Munoz et al. (2000) found no improvement in anxiety neither 3 nor 9 months of CPAP treatment. Moreover, in our study we revealed an association between hypoxic events and anxiety while Borak et al. (1996) observed correlation between fragmented sleep and anxiety.

It is still debated that fragmented sleep (Adams et al., 2001) or hypoxic events (Heinzer et al., 2001) or both cause the cognitive decrement in obstructive sleep apnea. In our study, we found that both sleep disruption and intermittent hypoxia can lead to cognitive deficit. We revealed that executive functions associated with increased slow wave sleep activity and decreased hypoxic events. In addition, hypoxic events showed association with short- and long-term episodic memory and anxiety level. Finally, sleepiness was correlated with executive functions and short-term verbal memory performance.

Conclusions

The following conclusion can be drawn based on the studies presented in this thesis:

1. We found dissociation between declarative and non-declarative memory functions in children with sleep-disordered breathing; the online declarative memory was decreased while the non-declarative form of learning was preserved in spite of intermittent hypoxia and sleep disruption.
2. We found intact consolidation in the case of declarative memory as well as sequence-specific and general skill aspects of non-declarative memory in children with SDB.
3. We can suggest that permanent sleep disturbances have less influence on implicit sequence-specific learning in childhood.
4. We revealed similar pattern of impairment in adult OSA patients as children with SDB; the working memory was impaired while the online implicit sequence learning was preserved in spite of hypoxia and sleep deprivation.
5. Our results are consistent with studies claiming no relationship between working memory and sequence learning.
6. More attention-demanding processes mediated by cortical structures (e.g. prefrontal and mediotemporal lobe) are influenced by hypoxia and disrupted sleep structure

while on the less attention demanding non-declarative processes mediated by subcortical structures (e.g. caudate nucleus, putamen) remain intact.

7. Regarding the consolidation of the two aspects of non-declarative memory in OSA patients we observed differences between the offline changes of general skill compared to controls; the control group showed offline improvement from evening to morning, thus they became faster in the morning after the offline period while the OSA group did not.
8. We failed to find differences between the OSA and control group not only in online sequence-specific learning but also in the consolidation of sequence-specific knowledge. It suggests that sleep might have less influence on this specific aspect of non-declarative learning.
9. Long-term sleep disturbances present in adult OSA patients play a differential role in the consolidation of the two aspects of non-declarative learning.
10. Short-term positive airway pressure therapy can improve the respiratory functions during sleep leading to improvement sleep patterns and reduced sleepiness.
11. Short-term PAP treatment restored anxiety level the cognitive functions such as working memory, short- and long-term verbal memory. However, despite treatment the long-term visual memory functions remain impaired.
12. Based on our results both intermittent hypoxia and fragmented sleep might can cause the cognitive decrement in obstructive sleep apnea.
13. Our findings suggest that cognitive dysfunction is at least partial reversible in OSA patients after short-term PAP therapy.

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Papers the thesis based on:

- I. Csábi, E., Benedek, P., Janacsek, K., & Nemeth, D. (2014). Sleep disorder in childhood impairs declarative but not nondeclarative forms of learning. *Journal of Clinical and Experimental Neuropsychology*, 35(7), 677-685.
- II. Csábi, E., Benedek, P., Janacsek, K., Zavec, Zs., Katona, G., & Németh, D. (2016). Declarative and non-declarative memory consolidation in children with sleep disorder. *Frontier in Human Neuroscience*, 9, 709.
- III. Németh, D., Csábi, E., Janacsek, K., Várszegi, M., & Mari, Z. (2012). Intact implicit probabilistic sequence learning in obstructive sleep apnea. *Journal of Sleep Research*, 21(4), 396-401.
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- IV. Csábi, E., Várszegi, M., Sefcsik, T., & Németh D. (2012). Effect of two month positive airway pressure therapy on the structure of sleep, cognitive function and anxiety. *Clinical Neuroscience/Ideggyógyászati Szemle*, 65(5-6), 181-194.

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Papers related to the thesis:

- I. Csábi E., Janacsek, K., Várszegi, M., & Nemeth D. (2011). Different effect of sleep on working memory and skill learning: cognitive function in sleep apnea. *Psychiatria Hungarica*, 26(2), 78-86.
- II. Csábi, E., & Nemeth, D. (2014). The role of sleep in the implicit learning processes. *Clinical Neuroscience*, 67(1-2), 9-18.
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- III. Csábi, E., Várszegi, M., Sefcsik, T., Janacsek, K., & Németh, D. The 5th International Conference on Memory (ICOM5), York, United Kingdom, July 31-August 5, 2011.
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