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Sleep disorder in childhood impairs declarative but not nondeclarative forms of learning

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A large amount of studies have investigated the association between sleep and memory systems. However, remarkably little is known of the effect of sleep disorders on declarative and nondeclarative memory for children. In the present study we examined the effects of sleep disorders on different aspects of memory functions by testing children with sleep-disordered breathing (SDB), which is characterized by disrupted sleep patterns. We used "The War of the Ghosts" test to measure declarative memory and the Alternating Serial Reaction Time (ASRT) task. This enabled us to measure two aspects of nondeclarative memory—general skill learning and sequence-specific learning—separately. Ten children with SDB and 10 healthy controls participated in this study. Our data showed dissociation between declarative and nondeclarative memory in children with SDB. They showed impaired declarative memory, while the sequence-specific and general skill learning was similar to that of healthy controls, in spite of sleep disruption. Our findings suggest that sleep-disordered breathing affects declarative and nondeclarative memory differently in children. Moreover, these findings imply that the disrupted sleep pattern influences the more attention-demanding and cortical structure-guided explicit processes, while the less attention-demanding implicit processes mediated by subcortical structures are preserved.

Keywords: Sleep; General skill learning; Sequence-specific learning; Declarative memory; Nondeclarative memory; Sleep-breathing disorder; Obstructive sleep apnea; Snoring.

Human learning and memory depend on multiple cognitive systems associated with distinct brain structures. Traditionally, declarative and nondeclarative memory systems are distinguished. Declarative memory is accessible to conscious recollection, including facts and episodes (for example, remembering events explicitly). It is defined by voluntary mechanisms that rely more on attentional resources and is thought to be mediated by frontal and medial temporal lobe structures. Nondeclarative memory relies more on automatic, nonconscious/implicit processes including

habituation, conditioning, and motor and perceptual skills (for example, playing the piano). It is primarily linked to frontostriatal networks (Cohen, Pascual-Leone, Press, & Robertson, 2005; Dennis & Cabeza, 2011; Doyon et al., 2009; Squire & Zola, 1996), while the hippocampus and medial temporal lobe structures can also be involved (Albouy et al., 2008; Schendan, Searl, Melrose, & Stern, 2003). These systems interact in cooperative and sometimes competitive ways to optimize memory and information processing performance (Poldrack et al., 2001; Poldrack & Packard, 2003). Previous

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studies in healthy children revealed that these two types of memory systems are differentially affected by sleep (Prehn-Kristensen et al., 2009; Wilhelm, Diekelmann, & Born, 2008). However, only one study investigated the effect of sleep disorders on declarative and nondeclarative memory systems at the same time in adults (Nemeth, Csábi, Janacsek, Varszegi, & Mari, 2012). In this study, patients with sleep disorders showed a lower working memory capacity, whereas the pattern of implicit learning was similar to that of healthy control subjects (Nemeth et al., 2012). As far as we know, no previous studies have examined this aspect among sleep-disordered children. Thus, we tried to fill this gap by exploring memory systems in children with sleep-disordered breathing (SDB).

There is a growing body of evidence that sleep contributes to the consolidation of memory by the enhancement of neural plasticity, which leads to the memory representation being more resistant to interference and forgetting (Diekelmann & Born, 2010; Diekelmann, Wilhelm, & Born, 2009; Stickgold & Walker, 2007). This view was confirmed in adults (Gais & Born, 2004; Walker, Brakefield, Morgan, Hobson, & Stickgold, 2002) but it is still unclear whether sleep contributes similarly to learning during development. Previous studies revealed that declarative memory consolidation benefits from sleep in children, but they did not find sleep-related improvement of nondeclarative memories (Backhaus, Hoeckesfeld, Hohagen, & Junghanns, 2008; Prehn-Kristensen et al., 2009; Wilhelm et al., 2008). Moreover, Fischer, Wilhelm, and Born (2007) showed a decreased performance in nondeclarative learning after sleep, suggesting that sleep plays a differential role for the processes of nondeclarative learning during childhood development compared with adulthood. These results indicate that sleep-dependent nondeclarative memory consolidation depends on age (Fischer et al., 2007; Wilhelm et al., 2008). Contrarily, few studies found similar performance in sequence learning between children with obstructive sleep apnea (OSA) and healthy control participants (Halbower et al., 2006; Hamasaki Uema et al., 2007). Furthermore, a recent study by Wilhelm, Metzkw-Mészáros, Knapp, and Born (2012) revealed that sleep induces the most robust gain in motor skills at an intermediate pre-sleep performance level. In low-performing children, sleep-dependent improvements in skill may be demonstrated only after enhancing the pre-sleep performance level by extended training (Wilhelm et al., 2012). To summarize these studies, we can conclude that sleep has significant effect on memory consolidation. However, less is known about how the permanent

sleep disruption influences the declarative and nondeclarative memory functions in general. Therefore the aim of our study was to investigate the functional status of children with sleep disorder.

Sleep-disordered breathing (SDB) is an ideal population to investigate the different effects of sleep disorder on declarative and nondeclarative memory processes. SDB is characterized by a broad spectrum of pathology, ranging from partial upper airway obstruction, such as primary snoring, to complete upper airway obstruction, such as obstructive sleep apnea (OSA). The etiology of SDB in children is multifactorial. Several medical conditions contribute to the development of SDB, including obesity, any anatomical abnormalities that narrow the upper airway (e.g., large tongue, hypertrophy of the adenoids or tonsils), and neuromuscular disorders (e.g., cerebral palsy, myotonic dystrophy; Arens et al., 2001; Guimaraes et al., 2008; Katz & D'Ambrosio, 2008; Sullivan, Li, & Guilleminault, 2008). Furthermore, local or systemic inflammation and syndromes with midface hypoplasia also predispose to SDB (e.g., Crouzon syndrome, Treacher Collins syndrome; Donnelly, Shott, LaRose, Chini, & Amin, 2004; Goldbart & Tal, 2008). The pathophysiology of SDB includes a decrease of the ventilatory drive and the upper airway muscle tone during sleep. This relaxed condition increases the collapsibility of upper airways and the resistance of air flow that is already narrowed by the above-mentioned causes. The collapse of pharyngeal airways leads to partial (hypopnea) or total airway obstruction (apnea), which disrupts the normal ventilation and sleep pattern during sleep (Coleman, 2003; Li & Lee, 2009; Mitchell, 2008; Sinha & Guilleminault, 2010). SDB is associated with a reduction in cognitive performance, such as attention, especially sustained attention rather than short-term attention, which may contribute to memory deficits (Beebe, 2006). Furthermore, SDB can cause a decrement in memory performance (Kheirandish-Goza, de Jong, Spruyt, Chamuleau, & Goza, 2010) and deterioration of executive functions (Beebe & Goza, 2002). For example, the former study by Kheirandish-Goza et al. (2010) investigated the acquisition and recall of declarative memory using a pictorial task in children with obstructive sleep apnea and healthy controls. They revealed that children with OSA showed decreased acquisition and recall performance compared to the control group. The authors suggested that this reduced performance may be caused by impaired ability to use adequate learning strategies, which leads to difficulties to learn new information or children with OSA suffering from impaired encoding or altered retrieval.

These decrements lead to decreased learning abilities, a deficit in general intelligence, and lower school performance (Beebe et al., 2004; Blunden, Lushington, Kennedy, Martin, & Dawson, 2000; Gottlieb et al., 2004; Kennedy et al., 2004; O'Brien, Mervis, Holbrook, Bruner, Klaus, et al., 2004; Salorio, White, Piccirillo, Duntley, & Uhles, 2002). Previous studies have found neurobehavioral deficits associated with snoring in children that are similar to those found in children with OSA (Gozal & O'Brien, 2004; O'Brien, Mervis, Holbrook, Bruner, Smith, et al., 2004). However, the mechanism causing these neuropsychological deficits has not been fully delineated. The long-term sleep fragmentation and oxygen deprivation might cause the dysfunction of memory and executive processes by disturbing the neuronal myelination and normal blood gas, which impacts the development of the brain, particularly in the hippocampus and frontal lobe structures (Bartlett et al., 2004; Halbower et al., 2006; Macey et al., 2002; Morrell et al., 2003). For example, Macey et al. (2002) revealed decreased gray matter in the hippocampus and frontal lobe in adult patients with OSA. The problem with behavioral regulation exhibited by children with SDB might also imply frontal lobe dysfunction. Frontal lobe function develops throughout childhood and is important for executive functions and attention-demanding tasks. In general, the damage to this region before the maturation of the prefrontal cortex could affect cognitive potential (Archbold, 2006; Beebe & Gozal, 2002; O'Brien et al., 2011).

The dissociation between declarative and non-declarative processes caused by long-term sleep disruption is clearly demonstrated in adults (Nemeth et al., 2012). The current study focuses on the developmental aspect of the effect of permanent sleep disturbances on different memory functions. We hypothesize that the frontal-lobe-related

executive functions and the attention-demanding declarative memory are affected by SDB, while the less attention-demanding nondeclarative learning functions remain intact.

METHOD

Participants

Twenty children participated in the experiment (Table 1). All participants underwent an overnight polygraphy, which was performed with the Somnomedics Somnoscreen plus device (Somnomedics, Randersacker, Germany) at the Sleep Disorders Laboratory of Heim Pál Children's Hospital, Budapest, Hungary. The SDB was diagnosed by a board-certified sleep physician. The SDB group consisted of 10 children with SDB (average age: 8.8 years, $SD = 1.68$; average education, i.e., average number of school years: 2.1 years, $SD = 1.66$: 5 females/5 males), 4 of them with OSA and 6 of them with primary snoring. According to the literature (Blunden et al., 2000; Kennedy et al., 2004; Montgomery-Downs, O'Brien, Cheryl, Holbrook, & Gozal, 2004), the main difference between the groups is the Snoring Index, $t(9) = 2.87, p < .01$ (0.1 vs. 11.00).

The control group consisted of 10 healthy participants matched by age and education (average age: 9.3 years, $SD = 2.45$; average education: 3.3 years, $SD = 2.54$; 7 females/3 males). They did not suffer from any developmental, psychiatric, or neurological disorders and were free of any sleeping disorders. Informed written parental consent and verbal assent of the children were provided, and participants did not receive financial compensation for their participation. Ethics approval was obtained by the Ethics Committee at Heim Pal Children's Hospital, Budapest.

TABLE 1
Sleep parameters, demographic data and executive functioning measures of the groups

	Control ($n = 10$)	SDB ($n = 10$)	t (df)	p
Age (years)	9.3 (2.45)	8.8 (1.68)	-0.531 (18)	.602
Sex female/male (n)	3/7	5/5		
Education (years)	3.3 (2.54)	2.1 (1.66)	-1.25 (18)	.22
BMI (kg/m^2)	16.64 (3.14)	15.77 (3.03)	-0.629 (18)	.53
AHI (events/hour)	0.14 (0.22)	1.96 (2.81)	2.037 (9.11)	.07**
Snore Index (events/hour)	0.1 (0.06)	11.00 (11.97)	2.87 (9)	.01**
TST (min)	464.11 (25.15)	473.1 (11.09)	0.988 (10.7)	.34
Letter fluency	8.4 (4.59)	5.6 (3.56)	-1.52 (18)	.14
Semantic fluency	14.2 (4.93)	13.5 (4.67)	-0.32 (18)	.74

Notes. Data are presented as mean, with standard deviations in parentheses, or %, unless otherwise stated. SDB = sleep-disordered breathing; BMI = body mass index, kg m^{-2} ; AHI = Apnea-Hypopnea Index: apneic and hypopneic events per hour of sleep; Snore Index = snoring events per hour; TST = total sleep time.

** $p < .05$.

Tasks

Alternating Serial Reaction Time (ASRT) task

We used a modified version of the original ASRT task in order to assess nondeclarative/implicit learning performance. In the original version of this task, four open circles were displayed in the middle of the computer screen, and subjects had to press the corresponding button when the circles were filled in with black (Howard & Howard, 1997). In our version, a dog's head appeared in one of the four empty circles on the screen, and the participants had to press the corresponding button (Nemeth et al., 2010). The computer was equipped with a special keyboard, which had four marked keys (Y, C, B, and M on a Hungarian keyboard), each corresponding to the circles. Before beginning the task, detailed instructions were read to the participants. We emphasized that the aim was to try to respond as quickly and as correctly as possible.

The ASRT consisted of 25 blocks, with 85 key presses in each block. The first five stimuli were random for practice purposes, then the eight-element alternating sequence (e.g., 2r1r4r3r, where numbers represent the four places on the screen, and r represents an event randomly selected from the four possible places) was repeated 10 times. Following Nemeth et al. (2010), stimuli were presented 120 ms following the previous response. As one block took about 1.5 min, the session took approximately 25–30 min. Between blocks, the participants received feedback about their overall reaction time and accuracy on the screen, then were given a rest of between 10 and 20 s before starting a new block.

A different ASRT sequence was selected for each participant based on a permutation rule so that each of the six unique permutations of the four repeating events occurred. Consequently, six different sequences were used across participants.

As there is a fixed sequence in the ASRT alternating with random stimuli (for instance, 2r1r4r3r), some triplets or runs of three stimuli occur more frequently than others. For example, in the above illustration, triplets **2_1**, **1_4**, **4_3**, and **3_2** would occur often because the third element (bold numbers) could be derived from the sequence or could also be a random element. In contrast, **1_2** or **4_1** would occur infrequently because in this case the third element could only be random. Following previous studies (Howard & Howard, 1997; Nemeth et al., 2010; Song, Howard, & Howard, 2007), we refer to the former as high-frequency triplets and

the latter as low-frequency triplets. Of the 64 possible triplets, the 16 high-frequency triplets occurred 62.5% of the time, and the 48 low-frequency triplets occurred 37.5% of the time. Note that the final event of high-frequency triplets is therefore more predictable from the initial event than the low-frequency triplets (also known as nonadjacent second-order dependency; Remillard, 2008).

Previous studies have shown that as people practice the ASRT task, they come to respond more quickly to the high- than low-frequency triplets, revealing sequence-specific learning (Howard et al., 2004; Howard & Howard, 1997; Janacsek, Fiser, & Nemeth, 2012; Nemeth et al., 2010; Song et al., 2007). In addition, general skill learning is revealed in the ASRT task by the overall speed with which people respond, irrespective of the triplet types. Thus, we are able to measure both sequence-specific and general skill learning in the ASRT task.

“The War of the Ghosts” test

Declarative memory performance was measured by “The War of the Ghosts” test (Bartlett, 1932; Bergman & Roediger, 1999; Marsh, 2007). This is a story recall test, which is widely used to measure episodic memory performance (Andreano & Cahill, 2006, 2008; Bergman & Roediger, 1999; Hardt, Einarsson, & Nader, 2010; Schwabe & Wolf, 2009). In this test, children are required to listen to a short story and then recall it immediately. The story consisted of 36 sentences; based on the standardized scoring, each sentence is allocated 1 point for the verbatim recalled sentences and 0.5 points for partly correct responses (gist recall; Bartlett, 1932; Gauld & Stephenson, 1967).

Procedure

We administered the “The War of the Ghosts” and ASRT task in one session between 19:00 and 21:00 both in SDB and in control groups. The order of the tasks was counterbalanced.

Statistical analysis

To facilitate data processing, the blocks of ASRT were organized into epochs of five blocks. The first epoch contained Blocks 1–5, the second epoch contained Blocks 6–10, and so on. We calculated mean accuracy and reaction time (RT) medians for correct responses only, separate for high- and low-frequency triplets and for each subject and each epoch. Note that for each response (n), we defined

whether it was a high- or a low-frequency triplet by considering whether it was more or less predictable from the event $n - 2$. For the analyses reported below, as in previous research (Howard & Howard, 1997; Nemeth et al., 2010; Song et al., 2007), two kinds of low-frequency triplets were eliminated: repetitions (e.g., 222, 333) and trills (e.g., 212, 343). Repetitions and trills were low frequency for all participants, and people often showed pre-existing response tendencies to them (Howard et al., 2004; Howard & Howard, 1997). By eliminating them we attempt to ensure that any high- versus low-frequency differences are due to learning and not to preexisting tendencies.

RESULTS

Accuracy analysis in the ASRT task

A mixed-design analysis of variance (ANOVA) was conducted on the five epochs of the data shown in Figures 1a and 1b with triplet (2: high vs. low) and

epoch (1–5) as within-subjects factors and group (SDB vs. control) as a between-subjects factor.

There was significant sequence-specific learning [indicated by the significant main effect of triplet: $F(1, 18) = 33.50$, $\eta_p^2 = .65$, $p < .001$] such that accuracy was greater on high- than on low-frequency triplets. SDB and control groups showed no differences in sequence-specific learning [Triplet \times Group interaction: $F(1, 18) = 0.02$, $\eta_p^2 = .002$, $p = .87$].

There was a trend in general skill learning [shown main effect of epoch: $F(4, 72) = 3.07$, $\eta_p^2 = .15$, $p = .07$] for accuracy to decrease across epochs. SDB and control groups performed at the same level [Epoch \times Group interaction: $F(4, 72) = 0.45$, $\eta_p^2 = .02$, $p = .58$].

The Triplet \times Epoch and Triplet \times Epoch \times Group interactions were not significant [$F(4, 72) = 1.43$, $\eta_p^2 = .07$, $p = .23$; $F(4, 72) = 1.73$, $\eta_p^2 = .08$, $p = .15$; respectively], indicating that the pattern of learning was similar in the groups. The main effect of group was not significant [main effect of group: $F(1, 18) = 0.66$, $\eta_p^2 = .04$, $p = .42$], reflecting that

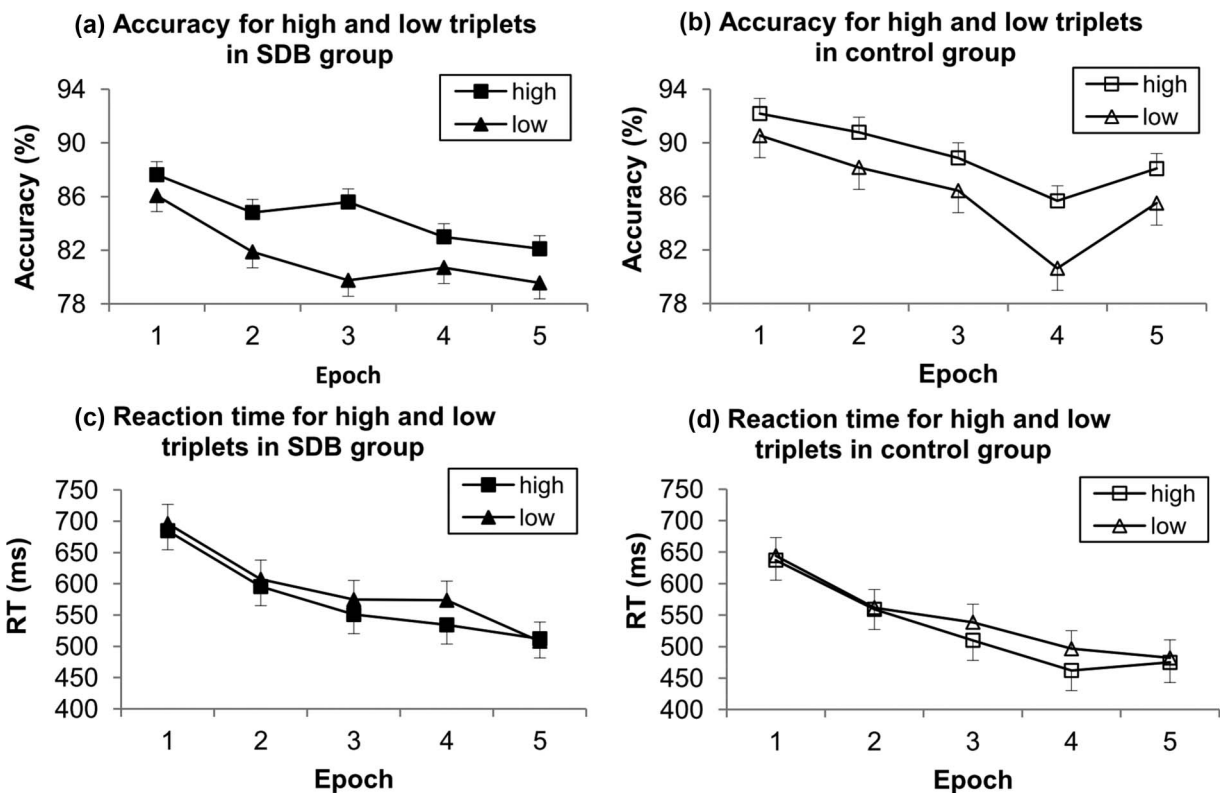


Figure 1. Results of accuracy for high and low triplets in (a) sleep-disordered breathing (SDB) and (b) control groups: Both groups showed significant sequence-specific learning, such that accuracy was greater on high- than on low-frequency triplets. There was a trend in general skill learning for accuracy to decrease across epochs in both groups. There were no differences between the groups: The pattern of learning was similar in the SDB and control groups. The results of reaction time (RT) for high- and low-frequency triplets in (c) SDB and (d) control groups are also plotted: Both groups demonstrated significant sequence-specific and general skill learning, such that RT was faster on high- than on low-frequency triplets, and the RT decreased across epochs. There were no significant differences between the groups: The pattern of learning was similar in the SDB and control groups. Error bars indicate standard error of mean (SEM).

all groups responded with similar accuracy rates (SDB group: 83%, control group: 87%).

Reaction time analysis in ASRT task

Similarly to the accuracy analysis, a mixed-design ANOVA was conducted on the five epochs of the data shown in Figures 1c and 1d with (triplet: high vs. low) and (epoch: 1–5) as within-subjects factors, and group (SDB vs. control) as a between-subjects factor.

Our data revealed significant sequence-specific learning [indicated by the significant main effect of triplet: $F(1, 18) = 38.57$, $\eta_p^2 = .68$, $p < .001$], such that RT was faster on high- than on low-frequency triplets. SDB and control groups showed no differences in sequence-specific learning [Triplet \times Group interaction: $F(1, 18) = 0.01$, $\eta_p^2 = .001$, $p = .92$].

There was also significant general skill learning [shown by the significant main effect of epoch: $F(4, 72) = 20.06$, $\eta_p^2 = .32$, $p < .001$], such that RT decreased across epochs, irrespectively of the triplet type. SDB and control groups performed at the same level [Epoch \times Group interaction: $F(4, 72) = 0.31$, $\eta_p^2 = .02$, $p = .66$].

The Triplet \times Epoch and Triplet \times Epoch \times Group interactions were not significant [$F(4, 72) = 2.07$, $\eta_p^2 = .10$, $p = .14$; $F(4, 72) = 0.16$, $\eta_p^2 = .009$, $p = .87$; respectively], indicating that the pattern of learning was similar in the groups. In the general reaction time, the SDB group did not differ significantly from the control group [main effect of group: $F(1, 18) = 1.09$, $\eta_p^2 = .06$, $p = .31$].

“The War of the Ghosts” test

In the case of the “War of the Ghosts” task, we used one-sample t tests to determine whether participants could recall significantly more sentences than zero, separately for the SDB and the control group. Then, the performances of the two groups were compared using an independent-samples t test.

The analysis revealed that both groups could recall sentences from the story, demonstrating a significantly better performance than zero [SDB group: $t(9) = 11.00$, $p < .001$; control group: $t(9) = 12.51$, $p < .001$]. Nevertheless, the declarative memory performance of the SDB group was significantly lower (7.7, $SD = 2.21$, vs. 14.7, $SD = 3.71$) than that of the control group, $t(18) = -5.12$, $p < .001$, Cohen’s $d = 2.36$ (Figure 2).

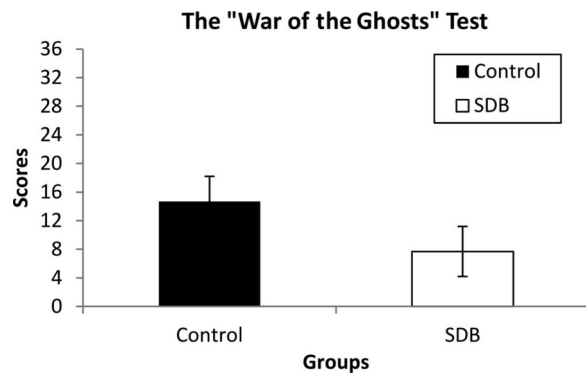


Figure 2. Declarative memory performance in sleep-disordered breathing (SDB) and control groups: The declarative memory performance of the SDB group was significantly lower than that of the control group. The dependent variable was the number of correctly recalled sentences. Error bars indicate standard error of mean (*SEM*).

DISCUSSION

Our goal was to investigate the effect of long-term sleep disturbances on declarative and nondeclarative memory functions in children with SDB. To examine nondeclarative memory we used the ASRT task, which allowed us to differentiate between general skill and sequence-specific learning. We found that children with SDB showed general skill learning and implicit learning of probabilistic sequences similar to that of healthy controls. In contrast, the SDB group demonstrated weaker declarative memory performance, measured by “The War of the Ghosts” test. Thus we found dissociation between declarative and nondeclarative memory functions.

Our results on declarative memory performance are similar to those of earlier studies showing weaker declarative memory performance in the SDB group (Blunden et al., 2000; Gottlieb et al., 2004; Kaemingk et al., 2003; Kennedy et al., 2004). Kennedy et al. (2004) found a direct relationship between the numbers of apneic/hypopneic events, oxygen desaturation, and the severity of neurocognitive deficits, with the greatest effect being on memory scores. The cause of this low memory performance can be linked to dysfunction of the frontal lobe (Cosentino et al., 2008; Thomas, Rosen, Stern, Weiss, & Kwong, 2005), as previous studies showed that the frontal lobe is the most vulnerable to sleep loss (Archbold, Giordani, Ruzicka, & Chervin, 2004; Jones & Harrison, 2001; Muzur, Pace-Schott, & Hobson, 2002).

We found similar performance between the SDB and the control group in general skill and sequence-specific learning, both in accuracy and in reaction time. Only a few studies have examined sequence

learning in childhood SDB, but our results are in line with previous work that found similar performance in learning function between children with OSA and healthy control participants (Halbower et al., 2006; Hamasaki Uema et al., 2007). To our knowledge, nondeclarative probabilistic sequence learning has never been tested in this patient population. We believed that the ASRT task allows the highest degree of specificity among available sequence learning tasks to study subcortical learning functions selectively, with the least cortical influence (Fletcher et al., 2005).

Our results are consistent with sleep deprivation studies in adults, which demonstrated weaker declarative knowledge, while the nondeclarative learning (serial reaction time; SRT) remained intact (Genzel, Dresler, Wehrle, Grözinger, & Steiger, 2009; Van Der Werf, Altena, Vis, Koene, & Van Someren, 2011; Wilson, Baran, Pace-Schott, Ivry, & Spencer, 2012). In our previous work, we also found impaired working memory, while the pattern of nondeclarative learning remained intact in patients with OSA (Nemeth et al., 2012). Moreover, these findings are similar to those of previous studies, which failed to find sleep-related improvement in nondeclarative memory processes in healthy children (Backhaus et al., 2008; Prehn-Kristensen et al., 2009; Wilhelm et al., 2008). Based on our results, we can suggest that permanent sleep disturbances have less influence on sequence-specific learning as well, not only in adulthood but also in childhood. In the declarative versus nondeclarative comparison, however, we cannot exclude the explanation that the lower performance on the declarative task was caused by fatigue and lower arousal because this type of memory depends on attentional resources to a higher extent than nondeclarative learning. Future studies need to clarify this issue.

Taken together, this study found dissociation between declarative and nondeclarative memory processes in children with SDB. The declarative memory was decreased, while the nondeclarative form of learning was preserved, in spite of permanent sleep disruption in SDB. These findings suggest that the more attention-demanding processes mediated by cortical structures (e.g., prefrontal and mediotemporal lobe) are influenced by disrupted sleep architecture, while the less attention-demanding nondeclarative processes mediated by subcortical structures (e.g., caudate nucleus, putamen) remain intact.

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