

The effect of Sleep-Disordered Breathing (SDB) on declarative and non-declarative memory processes in children and adults

Ph.D. Thesis

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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 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. A 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 the 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.

Összefoglalás

Egyre több bizonyíték támasztja alá, hogy az alvás szerepet játszik az emlékezeti konszolidációban azáltal, hogy ideje alatt olyan neurális változások következnek be az érintett agyi struktúrákban, melyek hozzájárulnak az emléknymok megszilárdulásához és hosszú távú rögzüléséhez. Keveset tudunk azonban arról, hogy az alvászavarok milyen hatással vannak a különböző emlékezeti komponensek működésére. Ezért disszertációmban négy olyan vizsgálatot mutatok be, amelyek az alvászavarok hatását vizsgálják eltérő emlékezeti rendszerek működésére felnőtt- és gyermekkorban. Az ötödik vizsgálat célja pedig az alvászavarok okozta kognitív funkcióromlás reverzibilitásának feltérképezése rövidtávú légsín terápia kezelését követően.

Az **első vizsgálatban** az alvászavar hatását vizsgáltuk a deklaratív és nem-deklaratív emlékezeti rendszerek működésére alvásfüggő légzésvizsgálatban szenvedő gyerekek körében. A **második vizsgálatban** pedig ennek a két típusú emlékezeti működésnek az alvás alatti konszolidációját szintén alvásfüggő légzésvizsgálatban szenvedő gyerekeknél. Eredményeink alapján az alvászavaros gyerekek alacsonyabb teljesítményt mutattak a deklaratív emlékezeti működésben az egészséges kontroll csoporthoz képest, azonban a nem-deklaratív emlékezeti működés megtartott. Az alvás alatti konszolidáció tekintetében intakt teljesítményt találtunk az alvásfüggő légzésvizsgálatban szenvedő gyereknél, mind a deklaratív, mind a nem-deklaratív emlékezet működésében, illetve ez utóbbi emlékezeti komponens két aspektusa, az általános készségtanulás és a szekvencia-specifikus tanulás esetében. A **harmadik vizsgálatban** a munkamemória és a nem-deklaratív emlékezeti működést vizsgáltuk felnőtt obstruktív alvási apnoés betegek körében egészséges kontroll csoporthoz viszonyítva. Eredményeink alapján nem találtunk különbséget az apnoés és a kontroll csoport között sem az általános készségtanulás, sem a szekvencia specifikus tanulásban, viszont a munkamemória teszteken az apnoés csoport lényegesen alulteljesített a kontroll csoporthoz képest. A **negyedik vizsgálatban** a nem-deklaratív emlékezeti működés alvás alatti konszolidációját vizsgáltuk szintén obstruktív alvási apnoe szindrómás betegeknél. Eredményeink azt mutatták, hogy a szekvencia-specifikus tanulás alvás alatti konszolidációjában nincs különbség az apnoés és a kontroll csoport között, azonban disszociációt találtunk az általános készségtanulásban a csoportok között. A kontroll csoport esetében javulás jelent meg estéről reggelre, amíg az apnoés csoportnál nem. Végül, az **ötödik vizsgálatban** az obstruktív alvási apnoe kezelésére alkalmazott légsín terápia kezelés hatékonyságát vizsgáltuk rövidtávon. Eredményeink alapján két és fél hónapos használatot követően jelentős javulás jelent meg az alvás alatti

légzésben, amely az alvásmintázat normalizálódását eredményezte. Ennek következtében csökkent a napközbeni aluszékonyosság. A kognitív funkciók tekintetében, javulást találtunk a komplex munkamemória, a rövid- és hosszú távú verbális és a rövidtávú vizuális emlékezeti működésben. Azonban, a kezelés ellenére a hosszú távú vizuális emlékezet romlást mutatott. A kezelés hatására javulás jelent meg az állapot szorongás szintjében, illetve tendencia szintű javulás mutatkozott a vonásszorongás szintjében. Mindemellett, összefüggést találtunk a mélyalvás és a végrehajtó funkciók között, valamint az alvás alatti hipoxiás epizódok mutatói, illetve a végrehajtó funkciók és az explicit emlékezet között.

Eredményeink hozzájárulhatnak ahhoz, hogy jobban megértsük az alvás szerepét az agy fejlődésében, illetve az emlékezeti reprezentációk hosszú távú rögzülésében. Mindemellett mélyebben megérthetjük, hogyan változik az életkorral az alvás és emlékezeti folyamatok közötti kapcsolat. Kutatásaink lehetőséget adnak arra, hogy általuk szofisztikáltabb diagnosztikus eszközöket hozzunk létre, illetve ennek révén egy pontosabb neuropszichológiai státuszt állítsunk fel, melyek egy hatékonyabb rehabilitációs program kidolgozásának első lépése lehet. Mindemellett eredményeink felhívják a figyelmet arra, hogy az alvás kevesebb szerepet játszhat az implicit folyamatokhoz kapcsolódó agyi struktúrák működésében.

1. Introduction

Currently, there are numerous theories about the function of sleep and why it is so essential for life. Firstly sleep is critical for the restoration of the body by reserving energy and regulating the energy expenditure. Sleep deprivation causes increased energy consumption whereas during sleep the basal metabolism is decreased by 15-20% (Lesku, Martinez-Gonzalez & Rattenborg, 2009; Susmakova, 2004). Secondly, sleep is essential for the restoration of the brain, principally the prefrontal and frontal lobe structures. The prefrontal cortex is the area of the brain that has the peak activity during the awake state. Therefore principally this area needs sleep in order to recover. The prefrontal cortex displays reduced activity during sleep and it appears functionally disconnected from other regions in the brain since in the awake state they would normally interact (Hobson, Stickgold & Pace-Schott, 1998; Maquet, 2000; Muzur, Pace-Schott & Hobson, 2002). Thirdly sleep plays a pivotal role in the development of the body as the release of growth hormone accounting for linear bone formation during early development, growth and maintenance of tissues through ontogeny, occurs predominantly in Non-Rapid Eye Movement (NREM) sleep in the first half of the sleep state (Hobson, 2009). Sleep is crucial in the brain development by during Rapid Eye Movement (REM) sleep as several brain areas reactivate to build up new synaptic relationships which are the basis of learning and the development of the brain. In addition, the myelination of nerve fibers also occurs during sleep (Hobson, 2009). Sleep plays a crucial role in the regulation of body temperature (Szymusiak, 2009) and immune functions (Mullington, 2009). Finally, there is a growing body of evidence that sleep is essential in learning and memory consolidation (Hobson, 2009; Sanes, Reh & Harris, 2006). This later function is the focus of my thesis.

1.1. Sleep-dependent memory consolidation

During awake state, a large amount of information is encoded in the brain, but we do not need to store any irrelevant information. The two-stage model of memory consolidation proposes that there are two separate memory stores (Diekelman & Born 2010; Diekelman, Wilhelm & Born, 2009). One of them allows fast learning, but stores the information temporarily, the other one account for slow rate learning and stores the information in a long term. The new information is encoded simultaneously in both stores. The next step of consolidation when the newly gathered information is repeatedly reactivated and processed in the fast and slow learning stores. Consequently, the new memories are gradually redistributed

becoming strong and stable representations in the long-term memory store. Both stores are used to encode information however, the reactivation and redistribution of new memories occur during sleep when no encoding takes place (Axmacher, Draguhn, Elger & Fell, 2009; Diekelman & Born, 2010).

During the awake state, the memory traces are encoded in the temporary (fast learning) and long term (slow learning) stores, represented by the hippocampus and neocortex, retrospectively. During subsequent slow wave sleep (SWS) the previously encoded information are repeatedly reactivated in both stores. This process is called system consolidation. This is where new memory representations in the network already pre-existing long-term memories is reorganized and integrated into the network. This system consolidation provides the background of synaptic consolidation during the ensuing REM sleep when the temporary and long-term stores disconnect from each other. This allows for locally encapsulated processes of synaptic consolidation when the new memory traces (are) strengthen and stabilize in a larger neuronal network containing the pre-existing memory representations (Born, Rasch & Gais, 2006; Diekelman & Born, 2010; Maquet, 2001; McClelland, McNaughton & O' Reilly, 1995; Stickgold, Hobson, Fosse & Fosse, 2001).

The functional background of memory consolidation is based on the reciprocal dialogue between the hippocampus and the neocortex. In the awake state, during the initial encoding, the information flows from the neocortex to the hippocampus. In subsequent sleep, the direction of information flow is reversed and transferred from the hippocampus to the neocortex (Buzsaki, 1996, 1998, 2002; Gais & Born, 2004; Marshall & Born, 2007; Stickgold et al., 2001). This sleep-related reconsolidation mechanism is required for the memory representations to become more resistant to interference and being forgotten.

1.2. The role of sleep in different memory systems

Human memory is not a single entity, it has been subject to several different classification schemes. One of the most popular categorization is based on the distinction between declarative and non-declarative memory (Squire, 1992, 1993, 2004). Declarative memory is considered as the consciously accessible - attentional demanding - memories of fact-based information ("knowing what"). Current neuronal model of declarative memory formation emphasizes the role of the medial temporal lobe, particularly the hippocampus and the frontal lobe structures. In contrast, non-declarative memory is regarded as the unconsciously accessible and less attentional demanding memories such as the learning of actions, habits and skills as well as implicit learning ("knowing how"). Most models and

empirical studies highlight that the underlying mechanism of implicit learning depends on diverse neuronal anatomies. For instance, implicit motor learning relates more to motor cortex and cerebellum, while the implicit sequence of learning is linked to the basal ganglia (Daselaar, Rombouts, Veltman, Raaijmakers & Jonker, 2003; Kincses et al., 2008; Rieckmann, Fischer & Bäckman, 2010). The role of the hippocampus, frontal and parietal areas remains inconclusive (Albouy et al., 2008, Gheysen, Van Opsal, Roggeman, Van Vaelwelde & Fias, 2010).

The beneficial effect of sleep in the hippocampus-dependent declarative memory is well demonstrated. A considerable number of studies demonstrated greater improvement on declarative memory task (word-pair list) after a period of sleep than after an equivalent time of wakefulness both in children (Backhaus, Hoeckesfeld, Hohagen & Junghanns, 2008; Prehn-Kristensen et al., 2010; Wilhelm, Metzkw-Mészáros, Knapp & Born, 2008) and adults (Gais, Mölle, Helms & Born, 2002; Gais, Lucas & Born, 2004; Ellenbogen, Payne & Stickgold, 2006/a; Ellenbogen Hulbert, Stickgold, Dinges, & Thomson-Schill, 2006/b; Racsmány, Conway & Demeter, 2010). Moreover,

The role of sleep in non-declarative/ implicit learning has not comprehensively described. In adults, ample body of studies found greater improvement in implicit sequence learning task after overnight sleep than after an equivalent time of being awake (Fischer, Hallschmid, Elsner & Born, 2002; Fischer, Nitschke, Melcher, Erdman & Born, 2005; Walker, Brakfield, Morgan, Hobson & Stickgold, 2002). In contrast, other studies failed to find sleep-related improvement in sequence learning (Nemeth et al., 2010; Rickard, Cai, Rieth & Ard, 2008; Rieth, Cai, McDevitt & Mednick, 2010; Urbain et al., 2013; Wilson, Baran, Pace-Schott, Ivry & Spencer, 2012). These controversial results might be explained by the variation in task complexity (e. g. sequence length and structure: motor learning or sequence-specific learning), type of the task (perceptual learning or motor learning), and the duration of the offline period (Csabi & Nemeth, 2014). In children, previous studies failed to find that sleep has a beneficial effect a facilitating on the non-declarative memory consolidation (Backhaus et al., 2008; Prehn-Kristensen et al., 2009; Wilhelm et al., 2008).

According to the two-step model or sequential theory, memory benefits optimally from the sequence of SWS and REM sleep (Ellenbogen et al., 2006/a; Smith, 2001). However, declarative memory benefits more from SWS-associated system consolidation. Sleep studies found a strong association between the improvement on declarative memory task and SWS in healthy participants (Gais & Born, 2004; Marshall, Mölle, Haschmid & Born, 2004; Marshall,

Helgadottir, Mölle, & Born, 2006; Marshall & Born, 2007; Takasima et al., 2006). Furthermore, REM sleep deprivation did not affect the performance on declarative memory task (Conway & Smith, 1994; Plihal & Born, 1997). The possible explanation of the relationship between declarative memory and SWS is the integrative nature of this type of memory. This means it binds features from different memories in different memory systems or the vigorous hippocampal-cortical, thalamocortical and cortico-cortical oscillatory activity during NREM supplies the declarative consolidation mechanism (Diekelman & Born, 2010; Ficca & Salzauro, 2004; Steriade, 2001; Steriade, Timofeev & Grenier, 2001). In contrast, non-declarative memory benefits more from REM sleep-associated synaptic consolidation marked by those studies which revealed an association between non-declarative performance and REM sleep (Cohen, Pascual-Leone, Press & Robertson, 2005; Smith, Nixon & Nader, 2004; Wagner & Born, 2008). The beneficial effect of REM sleep on non-declarative / implicit learning might be caused by the REM phase providing optimal milieu for the reactivation and long term storage of non-declarative material by several brain structures reactive during REM (e. g. anterior cingulate, caudal orbital and medial prefrontal cortices) (Braun et al., 1997; Muzur et al., 2002). In contrast, some studies emphasize the role of NREM 2 in the consolidation of non-declarative memory (Walker et al., 2002; Fogel & Smith, 2006). These studies observed greater impairment on non-declarative tasks after NREM 2 deprivation than REM restriction (Smith & MacNeill, 1994; Fogel & Smith, 2006). These results might be explained by the task complexity, namely, the relatively simple task involved in NREM 2, whereas REM sleep is required to process more complex task (Smith et al. 1994; Walker et al., 2002). However, there is increased the intensity of sleep spindles during NREM regardless of the learning material type (declarative or non-declarative). Thereby, it's an ideal indicator of both the information flow to the thalamus, neocortex and the consolidation processes (Clemens, Fabó & Halász, 2005; Genzel, Dresler, Wehrle, Grözinger & Steiger, 2009; Morin et al., 2009; Schmidt et al., 2006; Walker, 2009).

1.3. Effect of sleep deprivation on cognitive functions and memory in the healthy population

In light of the foregoing, optimal quality and quantity of sleep is essential for the optimal memory performance; however, studies that investigated the effect of sleep deprivation on different types of memory systems showed a mixture of results. Ample body of evidence indicates that sleep deprivation has an adverse effect on declarative memory performance such as recall for stories and words (Diekelman, Landolt, Lahl, Born & Wagner, 2008; Plihal & Born, 1997) and verbal learning (Drummond et al., 2000; Drummond, Meloy,

Yanagi, Orff & Brown, 2005; Yoo, Hu, Gujar, Jolesz & Walker, 2007). Tantawy, El Tallawy, Farghaly and Hussein (2013) demonstrated lower declarative memory performance (word-pair) after early-night SWS deprivation and after late-night REM sleep deprivation as well. They revealed that the left temporal lobe showed greater activity during memory retrieval after normal sleep, whereas the frontal, parietal and right temporal lobes were more active after sleep deprivation.

Only a few studies examined the effect of sleep deprivation on non-declarative / implicit memory consolidation. Some of these studies observed impaired implicit learning after sleep deprivation (e.g. Finger Tapping Task, Rotor Pursuit Task, Purdue Pegboard) (Buysse, Monk, Carrier, Berley, 2005; Heuer & Klein, 2003; Smith & MacNeill, 1994, Smith, 2001). Others found that implicit memory consolidation remains unaffected after sleep deprivation (Genzel et al., 2009). The lack of research and controversial results on this implicit learning field lead the focus of my thesis on the relationship between sleep and non-declarative memory consolidation.

Sleep deprivation studies have also show a negative effect on memory functions as well as in other cognitive domains such as working memory (Bartel, Offermeier, Smith & Becker, 2004; Choo, Lee, Venkatraman, Sheu & Chee, 2005; Plicher et al., 2007; Turner, Drummond, Salamat & Brown 2007), executive functions; including inhibition (Anderson & Platten, 2011; Chuah, Venkatraman, Dinges & Chee, 2006; Harrison & Horne, 1998), decisionmaking (Maddox et al., 2009; Venkatraman, Chuah, Huettel & Chee, 2007), logical reasoning (Drummond, Brown, Salamat & Gillin, 2004), error detection (Nilsson et al., 2005; Tsai, Young, Hsieh & Lee, 2005), mental flexibility and switching (Stenuit&Kerkhofs, 2008; Van Dongen, Maislin, Mullington&Dinges, 2003). The vigilance and attention impairment suggested by several studies might give an explanation to the deterioration of other cognitive domains following sleep deprivation (Blatter et al., 2006; Drummond, Gillin & Brown, 2001; Van Dongen et al., 2003).

Neuroimaging studies on sleep deprivation have shown that changes in cerebral activation are associated with changes in cognitive performance. These studies demonstrated that brain regions activity during cognitive tasks after sleep deprivation differ from having normal sleep (Bell-McGinty et al., 2004; Chee et al., 2006; Drummond et al., 1999; Thomas et al., 2000; Tomasi et al., 2009; Wu, Buchsbaum & Bunney, 2001). A decrease in cerebral activity has been observed primarily in the thalamus, temporal, prefrontal and parietal cortices

after sleep deprivation (Chee et al., 2006; Drummond et al., 2000; Drummond et al., 2001; Thomas et al., 2005; Tomasi et al., 2009; Wu et al., 2001).

Several explanations have been proposed to explain the impact of sleep deprivation on cognitive functions. For instance, the vigilance hypothesis proposes that interaction between the need for sleep and circadian factors causes fluctuating levels of arousal, which destabilize the neuronal and cognitive performance (Doran, Van Dongen & Dinges, 2001). Another explanation suggests that sleep restriction impacts on the efficiency of prefrontal cortex and produces changes in cerebral activity which leads to changes in cognitive functioning (Beebe & Gozal, 2002; Harrison & Horne, 2000). Furthermore, the compensatory adaptation hypothesis proposes that sleep deprivation results in a global rather than a localized brain alteration, particularly in the parietal lobes and thalamus. This hypothesis can explain those studies which found that the executive functioning after sleep loss is preserved. Finally, fMRI (functional magnetic resonance imaging) studies of sleep deprivation also confirmed the functional changes of several brain regions besides the frontal lobe after sleep loss (Chee & Choo, 2004; Tucker et al., 2010).

2. Sleep-Disordered Breathing (SDB) in children

2.1. Definition, classification, prevalence and risk factors of SDB

Sleep-disordered breathing is a spectrum of disorders which ranges from partial upper airway obstruction such as primary snoring to complete upper airway obstruction such as obstructive sleep apnea (OSA) (American Academy of Sleep Medicine, 2001; Sinha & Guilleminault, 2010). Primary or habitual snoring occurs when the soft palate or pharyngeal tissues vibrate without oxygen desaturation, hypoventilation, and episodes of apnea or arousals from sleep (Garetz, 2007; Melendres, Lutz, Rubin & Marcus, 2003). SDB also includes OSA, which is characterized by prolonged partial upper airway obstruction (hypopneas) or complete upper airway obstruction (apnoea) during sleep, oxygen desaturation and hypercapnia (American Academy of Sleep Medicine, 2001; Kuhle, Urschitz, Eitner & Poets, 2009).

Polysomnography (PSG) is the gold standard for diagnosis of SDB in children. The standard parameters that can be obtained from polysomnography include: sleep architecture, respiration, cardiac rhythm, muscle activity, gas exchange and snoring (Li & Lee, 2009). The most important index that defines the severity of OSA is the Apnea-Hypopnea Index (AHI) which is computed from the number of apneas and hypopneas per hour of total sleep time (American Academy of Sleep Medicine, 2001). The International Classification of Sleep

Disorders 2nd Edition (ICSD-2) defines apnea as an absence of airflow with continued chest wall and abdominal wall movement for the duration longer than two breaths (American Academy of Sleep Medicine, 2001). The definition of hypopnea as a reduction in airflow by at least 30% from baseline with or without oxygen desaturation by more than 3% and/or arousals (Johnson & Roth, 2006; Marcus, 2001). The severity of OSA was classified on the basis of AHI. Children incidence of AHI greater than 1 per hour of sleep were classified as having mild OSA, those with AHI from 1 to 5 classified as moderate OSA and those with AHI greater than 5 per hour of sleep classified as severe OSA (Amin et al., 2003, Katz et al., 2002; Verhulst et al., 2007).

Prevalence of OSA in children has been reported to be between 1% and 3%, and 10% or more in children that are habitual snorers (Castronovo et al., 2003, Gottlieb et al., 2004, Mitchell, 2008; Sinha & Guilleminault, 2010). The main factors predisposing to SDB can be broadly divided into two regions: the first are anatomical causes that reduce upper airway lumen size such as adenotonsillar hypertrophy, craniofacial factors (e. g. small or retroposition mandible, large or retroposition tongue) (Sinha & Guilleminault, 2010; Tan, Gozal & Kheriandish-Gozal, 2013). The second are also anatomical factors that promote increased upper airway collapsibility which include altered neurological upper airway reflexes, hypotonia and upper airway inflammation (Arens et al., 2011; Katz & D' Ambrosio, 2008; Guimaraes et al., 2008). Obesity also contributes to the development SDB, because fatty infiltrates deposited in the pharyngeal structures result in a reduced upper airway volume (Kohler & Van den Heuvel, 2008; Tan et al., 2013). Few studies revealed that OSA is more common in African-American children, due to either structural differences or socioeconomic factors (Rosen et al., 2003; Saxena, Ambler, Cole & Majeed, 2004).

2.2. Pathophysiology, clinical symptoms of SDB

In adults OSA, is commonly associated with obesity. Obese children are also at risk for SDB however, most children with OSA are not obese. The vast majority of cases of OSA in children are associated with adenotonsillar hypertrophy (Gozal & Burnside, 2004; Marcus et al., 1996; Marcus et al., 2001). The pathophysiology of SDB includes a decreased in ventilatory drive and loss of upper airway muscle tone during sleep. This relaxed condition increases the collapsibility of upper airways and the resistance of airflow which is already narrowed by the aforementioned anatomical abnormalities. The occlusion of pharyngeal airways leads to partial or complete airway obstruction and increased respiratory effort or decreased in the central respiratory drive which disturbs normal ventilation and normal sleep

pattern (Kohler et al., 2008; Marcus, 2001; Tan et al., 2013). Some studies have found that apnea-related arousals are less commonly in children and instead subcortical arousals are more frequently present as demonstrated by movements, resulting in better-preserved sleep architecture (Goh & Galster, 2000; Mograss, Ducharme & Brouillette, 1994).

The most important clinical symptoms in pre-school and school-aged children indicating SDB can be divided into nighttime and daytime symptoms. The main nighttime symptoms are snoring, witnessed apneas, frequent arousals, dry mouth, nocturnal sweating, nasal congestion, drooling and enuresis. The most important daytime symptoms are confusional arousal, hyperactivity, inattention, morning headache and difficulty waking up (Li & Lee, 2009; O' Brien et al., 2011; Sinha & Guilleminault, 2010). Cortical arousals occur less frequently in children with SDB in contrast to adults therefore, they have a less fragmented sleep. Consequently, daytime sleepiness is an uncommon symptom in pediatric OSA (Halbower & Mahone, 2006; Tan et al., 2013).

2.3. Cognitive and behavioral consequences

SDB-associated cognitive performance impairment is consistently apparent in tasks involving attention and executive functions (Archbold, Giordani, Ruzicka & Chervin, 2004). Several studies found reduced selective and sustained attention on Continuous Performance Task (CPT) (Archbold et al., 2004; Avior et al., 2004; Blunden, Lushington, Kennedy, Martin & Dawson, 2000; Huang et al., 2004). Similarly, it was also found on the visual subtest of the Developmental Neuropsychological Assessment (NEPSY) compared with the control subjects (O' Brian et al., 2004a; O' Brian et al., 2004b).

Most of the studies emphasized executive dysfunctions in SDB including the working memory and mental flexibility (Archbold et al., 2004), inhibition and planning (Karpinsky, Scullin & Montgomery-Downs, 2008). Executive functions are a heterogeneous set of skills (e. g. behavioral inhibition, set-shifting, self-regulation) that are believed to be important in high level and goal-directed adaptive functioning (Beebe, Groesz, Wells, Nichols & McGee, 2003). Halbower et al. (2006) used MRSI (Magnetic Resonance Spectroscopy Imaging) to observe the metabolic alterations of the brain. This revealed that children with OSA exhibited impaired executive functioning and abnormal metabolites were present in the hippocampus and the right frontal cortex indicating possible brain injury. Frontal lobe functions develop throughout childhood (Beebe & Gozal, 2002), thus, the damage to this region before the maturation of the prefrontal cortex could affect executive functions, cognitive potential, and behavior. The behavior regulation problems (e.g. aggressive behaviors, impulsiveness,

irritability, and hyperactivity) exhibited by children with SDB might suggest frontal lobe dysfunction (Archbold, 2006). Several studies found an association between SDB and Attention Deficit and Hyperactivity Disorder (ADHD) (Barnes et al., 2009; Barnes, Gozal & Molfese, 2012; Beebe, 2013). Moreover, Golan, Shahar, Ravid & Pillar (2004) found that 19% - 50% of children with ADHD were diagnosed with OSA following PSG compared to healthy control subjects. Besides the explanation of frontal cortex-guided executive dysfunction, Weinberg and Harper (1993) suggest the hyperarousal theory as a possible underlying mechanism for ADHD. According to this theory, children with ADHD are in fact sleepy and use the excessive motor activity as a method to stay awake.

Studies testing memory function in children with SDB are scarce and they yield mixed results. Some of the studies found impaired verbal and visual memory performance measured by Wilde Range Assessment of Memory and Learning (WRAML) tasks battery (Rhodes et al., 1995; Blunden et al., 2000). A recent study by Kheirandish-Gozal et al. (2010) suggested that a reduced verbal memory performance may be caused by an impaired ability to use adequate learning strategies; this can lead to difficulties in learning new information, or impaired encoding or altered retrieval in children with OSA. In contrast, other studies failed to find differences between verbal memory performance between children with SDB and healthy controls subjects (O' Brien et al., 2004a; O' Brien et al., 2004b; Owens, Spirito, Marcotte, McGuinn & Berkelhammer, 2000). An explanation behind these controversial results might be because some aspects of memory such as memory acquisition and repetition are negatively affected by sleep deprivation and / or hypoxia (Kaemingk et al., 2003). Furthermore, we cannot exclude the theory that impaired executive function may have an adverse effect on the task of other neurocognitive domains (Gottlieb et al., 2004). It is still controversial how the cognitive impairment could be related to disease severity. A number of studies indicate, that cognitive dysfunction is more pronounced in severe SDB than in mild level of SDB or primary snoring (Blunden et al., 2000; Lewin et al., 2002; Smejde, Broman & Hetta, 2001). In contrast, other studies fail to find relationships between cognitive functions and disease severity (Owens et al., 2000).

Several studies report that cognitive and behavioral consequences of SDB lead to lower IQ (Intelligence Quotient) scores (obtained for the Wechsler Intelligence Scale for Children) (Beebe et al. 2004; Blunden et al., 2000, Gottlieb et al., 2004; Halbower et al., 2006) and reduced academic performance (Carvalho et al., 2005; Chervin et al., 2003; Curcio, Ferrara & De Gennaro, 2006; Perez-Chada et al., 2007). The underlying mechanism causing the lower

level of IQ and academic performance in SDB has not been fully delineated. Some authors suggest that impaired executive functions are crucial for good school performance (Blunden et al., 2000; Lewin, England & Rosen, 1999). Other studies propose that adequate sleep may be important for the consolidation of memory which could have positive impact in academic success (Carkasdon, Acebo & Jenni, 2004, Stickgold, 2005). Moreover not all children with OSA exhibit intellectual or behavioral deficits, this raises the possibility that individual genetic susceptibility and environmentally dictated changes in the susceptibility to disease may play a significant role in the phenotypic presentation of any given child (Kheirandish & Gozal, 2006). In addition, it remains unclear whether sleep-disordered breathing has a direct effect on learning or the impaired academic achievement is a phenomenon secondary to behavioral disturbances (e. g. ADHD).

The mechanism explaining neurocognitive deficits and behavioral disturbances in children with SDB is unclear. Several studies suggest that one primary mechanism causing cognitive dysfunctions in SDB is intermittent hypoxia leading to structural and neurochemical changes in the brain, particularly in the hippocampus and prefrontal cortex, which are especially involved in attention and executive functions (Gozal et al., 2002; Row, Liu, Kheirandish & Gozal, 2003; Shan et al., 2007; Xu et al., 2004). In addition, there is evidence which suggest that repeated episodic arousals from sleep have negative influences on cognitive functions. According to sleep studies, REM and NREM sleep integrity is necessary to the long-term storage of memory traces, thus the disruption of this sleep stages may interrupt or reduced the efficiency of processes underlying memory consolidation (Diekelman & Born, 2010). Moreover, sleep fragmentation alters the restorative features of sleep, disturbs normal sleep architecture and causes sleepiness (Beebe & Gozal, 2002; Fallone, Owens & Deane, 2002). These findings support those studies on sleep deprivation which demonstrated that sleep is of particular importance for restorative prefrontal cortex-guided functions (Cajohen, Knoblauch, Kräuchi, Renz & Wirz-Justice, 2001; Finelli, Borbely & Achermann, 2001). The findings of the studies can be explained by the idea that the prefrontal cortex is the hardest-working cortical region of the brain in the awake state, therefore, this area primarily needs sleep to recover. The prefrontal cortex displays reduced activity during sleep and appears functionally disconnected from other regions with which it normally interacts with in waking (Hobson et al., 1998; Maquet, 2000). In contrast, some studies found impairments in spatial memory functioning and academic achievement in where there is absence of significant sleep fragmentation or deprivation (Gozal, Daniel & Dohanich, 2001; Payne,

Goldbart, Gozal & Schurr, 2004; Schlaud et al., 2004; Urschitz et al., 2003; Urschitz et al., 2004; Urschitz et al., 2005). To clarify these contradictions, some studies suggest that hypoxia and fragmented sleep affects different cognitive functions. Both mechanisms may cause alteration in the metabolism and neurochemistry of the brain; however hypoxia may result in selective impairments in executive processes while sleep fragmentation may preferentially have an affect attention (Blunden et al., 2000; Bedard, Montplaisir, Richter, Rouleau & Malo, 1991; Kaemingk et al., 2003; Naegele et al., 1995). We cannot exclude the negative effect of sleepiness on cognitive functioning, but sleepiness is relatively uncommon in children with SDB and the effects of sleepiness are often displayed behaviorally (e. g. hyperactivity, impulsivity, aggression) rather than verbally (e. g. complaining of being tired) (Chervin et al., 1997; Fallone et al., 2002; Owens, 2009). Thus, sleepiness is an important sign of SDB particularly in adults, but its effect is reversible with sleep recovery.

3. Obstructive Sleep Apnea Syndrome (OSAS/OSA) in adults

3.1. Definition, diagnosis and classification of OSA

According to the International Classification of Sleep Disorders - 2nd Editions (ICSD-2), OSA belongs to the sleep-related breathing disorders characterized by repetitive episodes of complete or partial upper airway obstruction during sleep resulting in hypoxia and fragmented sleep (American Academy of Sleep Medicine, 2001). The ICSD-2 has defined two major categories of SDB: central sleep apnea syndrome (CSAS) and obstructive sleep apnea syndrome (OSA). The difference between the major categories is the pathophysiological mechanism that causes the respiratory disturbance. CSAS involves the dysfunction of ventilatory control in the central nervous system while in OSA the upper airway obstruction causes the abnormal respiration during sleep (American Academy of Sleep Medicine, 2001).

The severity of OSA was classified on the severity of sleepiness and AHI index (see Chapter 2.1.). It is classified as mild, moderate and severe. Mild OSA is defined as abnormal sleepiness or involuntary sleep episodes during activity requiring little attention (e.g. watching TV, reading) and AHI 5-15 events/hour. Moderate OSA is characterized by abnormal sleepiness or involuntary sleep episodes during activity requiring some attention (e. g. meeting, concerts) and AHI 15-30 events/hour. In the case of severe OSA the AHI exceeds 30 events per hour and abnormal sleepiness or involuntary sleep episodes appear during activity requiring active attention (e. g. during a conversation, driving) (American Academy of Sleep Medicine; 2001; Banno & Kryger, 2007).

3.2. Prevalence and risk factors of OSA

The prevalence of OSA is approximately 3-7% in adult men and 2-5% in adult women (Pataka & Riha, 2009; Punjabi, 2008). In contrast to children, the majority of adult patients with OSA are obese. In obesity, the excess fat tissue around the neck contributes to the narrowing of the airways. This increases extraluminal pressure on the pharyngeal structures and increases the risk of upper airway obstruction (Crummy, Piper & Naughton, 2008; Schwartz et al., 2008; Young, Peppard & Gottlieb, 2006/a). Craniofacial abnormalities also predispose adults to OSA (e.g. retrognathia, tonsillar hypertrophy, enlarged tongue or soft palate) (Pataka & Riha, 2009). The incidence of OSA increases with age due to the increased deposition of fat in the parapharyngeal region, the elongation of the soft palate and age-related changes in structures surrounding the pharynx (Eikermann et al., 2007; Young et al., 2002/b). There is also evidence that OSA is more frequent in African-Americans than in Caucasians presumably due to the structural differences in the soft tissues and bony structures of the upper airways (Malhotra & White, 2002; O' Connor et al., 2003). OSA occurs more commonly in males due to the differences in craniofacial morphology and functional anatomy of the upper airways and different ventilatory responses to arousals from sleep (Jordan & McEvoy, 2003; Pillar et al., 2000). Moreover, the upper body fat deposition is more prevalent in males (Jordan & McEvoy, 2003). The hormonal status may affect the respiratory function in both genders, thus hormonal influence plays an important role in the development of abnormal breathing during sleep (Ye, Pien & Weaver, 2009). Some social habits have also been identified as risk factors for OSA including smoking, alcohol and sedative consumption (Franklin et al., 2004; Peppard, Austin & Brown, 2007).

3.3. Pathophysiology, clinical symptoms and comorbidities of OSA

The main factors predisposing to OSA in adulthood are obesity and craniofacial abnormalities which increase the risk of the upper airway obstruction (Malhotra, Pillar, Fogel, Beauregard & White, 2000; Malhotra & White, 2002). The key pathophysiological mechanism in OSA is a compensatory negative pressure reflex that is triggered by the abnormal anatomy and increases the activity of pharyngeal dilators. After the onset of sleep the loss of negative pressure reflex and decreased pharyngeal dilator tone leads to upper airway collapse. The repetitive episodes of upper airway obstruction during sleep bring about hypoxia and hypercapnia and lead to increased respiratory effort and repeated arousals from sleep disturbing the ventilation and normal sleep pattern (Banno & Kryger, 2007; Bradley & Floras, 2009; Fleisher & Krieger, 2007). The clinical presentation of OSA in adulthood also

can be divided into symptoms in awake and sleep state similarly to childhood SDB. The main symptoms during sleep are observed apneas, snoring, frequent awakening, gasping, choking and sweating. The most important symptoms when awake are: excessive daytime sleepiness, fatigue, morning headache, dry mouth and gastroesophageal reflux (Banno & Kryger, 2007; Bradley & Floras, 2009).

Without effective treatment, OSA can lead to systemic hypertension, pulmonary hypertension, cardiovascular (e.g. arrhythmia, myocardial infarction and congestive heart failure) and cerebrovascular complications such as stroke (Fletcher, McNicholas & Bonsignore, 2007; Peppard et al., 2000; Yamakawa et al., 2002; Zafarlofti, Quadri & Borodovsky, 2010). Some studies suggest that OSA may cause insulin resistance and type 2 diabetes mellitus. It is not entirely clear whether OSA or obesity results in metabolic disease, as insulin resistance is strongly associated with obesity which is common in OSA (Brooks et al., 1994; Ip et al., 2002; Strohl et al., 1994; Vgontzas, Bixler & Chrousos, 2005).

3.4. Cognitive and affective consequences of OSA

Similarly to children with SDB, most of the studies emphasized that there are vigilance and attentional deficit in patients with OSA measured by Continuous Performance Task (Aloia, Arnedt, Davis, Riggs & Byrd, 2004; Kotterba et al., 1998; Mazza et al., 2005; Redline et al., 1997; Verstraeten, Cluydts, Pevernagie & Hoffman, 2004). Event-related potential (ERP) studies demonstrated prolonged P300 latency on deviant stimuli in OSA patients, this means that their attentional resources are delayed and persistently longer than those of control subjects (Gosselin et al., 2006/a; Gosselin et al., 2006/b). Gosselin et al. (2006/b) suggest that this dysfunction is linked to frontal lobe deficit. Some studies proposed that vigilance and attentional deficit play a pivotal role in all aspects of cognitive deficits noted in OSA (Mazza et al., 2005; Verstraeten, et al., 2004). The executive dysfunction is well-described in patients with OSA. It is measured by different tasks such as Wisconsin Card Sorting, Tower of Toronto, Stroop Color Test (Lee, Strauss, Adams & Redline, 1999; Naegele et al., 1995), Trailmaking Task (Bedard et al., 1991; Cheshire et al., 1992), verbal fluency task (Kim et al., 1997) and Go-No-Go Task (Sagaspe et al., 2007).

Most of the studies found impaired memory functions in patients with OSA including working memory (Cosentino et al., 2008; Naegele et al., 2006) as well as short- and long-term and verbal and visual memory (Pierobon et al., 2008; Salorio et al., 2002). Functional MRI studies found that retrieval processes produced greater right prefrontal cortical activation

(Nyberg et al., 1996; Tulving, Kapur, Craik, Moscovitch & Houle, 1994) which seems to be affected by OSA.

Few studies have examined implicit sequence learning in patients with OSA and these results are controversial. Some of them revealed intact performance on Finger Tapping (Archbold et al., 2009; Wild et al., 2007) and Rotor Pursuit Task or Mirror Tracing Task (Rouleau, Decary, Chicoine & Montplaisir, 2002). By contrast, Lojander et al. (1999) observed poorer performance on the same tasks in patients with apnea. A small number of studies examined the overnight consolidation of the acquired implicit knowledge. These studies observed that OSA patients and those in the control group displayed almost identical performance during the initial learning in the evening, however the control group exhibited significantly more overnight improvement on implicit motor learning task (Finger Tapping, Mirror Tracing) (Djonlagic, Saboisky, Carusona, Stickgold & Malhotra, 2012; Kloepfer et al., 2009). The association between the severity of OSA and cognitive impairment is still controversial. Several studies noted a distinct trend toward increasing cognitive impairment with increasing AHI (Apnea-Hypopnea Index) (Aiola et al., 2004, Engleman et al., 2000; Kamba et al., 2001; Sateia, 2003) while others failed to find correlation between the severity of OSA and cognitive dysfunction (Naegale et al., 2006; Redline et al., 1997; Solorio, White, Picirillo, Duntley & Uhles, 2002).

OSA patients commonly showed psychiatric syndromes such as depression, anxiety, somatization, obsession-compulsion and hostility (Aikens, Caruana-Montaldo, Vanable, Tadimeti & Mendelson, 1999; Aloia et al., 2005, Borak et al., 1996; Yue et al., 2003). Naismith, Winter, Gotsopoulos, Hickie & Cistulli (2004) and Sforza, De Saint Hilaire, Pelissolo, Rochat & Ibanez (2002) suggest that the severity of depression and anxiety appear to be reflected more on the degree of daytime sleepiness rather than on the degree of nocturnal hypoxia. Female with OSA had higher anxiety and depression scores independent of other factors than male (Cassel, 1993; Phillips et al., 1996).

3.5. The effect of hypoxia and fragmented sleep

The causal mechanism of cognitive impairments remains open to debate. Several researchers have argued that nocturnal hypoxia causes the cognitive decline in OSA patients by disturbing alteration of the brain (Adams, Strauss, Schluchter & Redline, 2001; Bedard, Montplaisir, Malo, Richer & Rouleau, 1993; Kheirandish, Gozal, Pequignot, Pequignot & Row, 2005/a; Kheirandish, Row, Li, Brittan & Gozal, 2005/b; Kim, Dinges & Young, 2007; Van Dongen, Baynard, Maislin & Dinges, 2004). In contrast, other studies emphasized that

the cognitive dysfunction in OSA associated with disturbed sleep leads to excessive daytime sleepiness which can contribute to decreased performance on neuropsychological tests in itself (Cohen-Zion et al., 2004; Thomas et al., 2005; Thomas et al., 2007; Verstraeten, 2007). Moreover, fragmented sleep precludes the effective consolidation of relevant information during sleep (Buzsaki, 1996; Kavanau, 1998; Maquet, 2001; Stickgold, 1998). Recent studies indicate that hypoxia and disrupted sleep are differentially related to the cognitive decline associated with OSA (Adams et al., 2001; Bedard et al., 1993; Naegele et al., 1995). According to these studies, excessive daytime sleepiness is mainly related to reduced attention and memory functions (Bedard et al., 1991), while hypoxia contributes to the deficit in different aspects of executive functioning (Block, Berry & Webb, 1986; Cheshire et al., 1992; Findley et al., 1986). Beebe and Gozal (2002) propose that the effect of OSA on prefrontal dysfunction is mediated by a disruption in the restorative feature of sleep and by a structural or chemical aberration. The prefrontal cortex is the hardest working cortical brain region in awake state which requires sleep to recover, because the recalibration of this area occurs during sleep as it is showed by its reduced activity and disconnection from other brain regions (Hobson et al., 1998; Harrison & Horne, 2000; Finelli et al., 2001; Gozal, 2008; Maquet, 2000). Beebe and Gozal (2002) propose that sleep disruption and intermittent hypoxia reduce the efficiency of sleep-related restorative processes and this leads to disruption of the functional homeostasis of the central nervous system and alters neuronal and glial viability in certain regions. Subsequent dysfunction of prefrontal regions manifested in executive dysfunctions alters the functional recruitment of more primary cognitive abilities resulting in maladaptive daytime behaviors.

There is a growing body of evidence which demonstrates the structural brain damages in OSA patients. MRI studies observed regional gray matter loss in multiple brain sites including the hippocampus, cerebellum, frontal and parietal cortex and anterior cingulate. These areas are involved in the motor regulation of the upper airways and cognitive processing (Macey et al., 2002; Morell et al., 2003). Torelli et al. (2011) revealed that the volume of cortical gray matter, right hippocampus, right and left caudate were smaller in OSA patients compared to those without OSA. Some studies suggest that the degree of brain damage correlates with the severity of OSA (Kamba, Suto, Ohta, Inoue & Matsuda, 1997; Kamba et al., 2001).

3.6. Treatment of OSA

One of the most effective treatments for OSA is nasal continuous positive airway pressure (CPAP) or bilevel positive airway pressure (BiPAP) therapy during sleep (Lin, Chuang, Liao, Chen & Li, 2003; Olsen, Smith & Oei, 2008; other modes of treatment see in e. g. Malhotra & White, 2002; Fleisher & Krieger, 2007). The Positive Airway Pressure (PAP) machines treat sleep apnea by the emission of a prescribed pressure of air. This emission of air operates as a pneumatic splint and maintains the airways open. Patients who use PAP machines are required to wear a mask attached to a hose during sleep (Haynes, 2005; Sullivan, Issa & Berthon-Jones, 1981).

Most of the studies emphasized the immediate and long-term beneficial effect of (CPAP/Bi) PAP therapy on sleep quality via recovery processes of sleep and ventilation during sleep. These studies reported that treatment with short-term CPAP therapy results in reduced sleep latency and percentage of light sleep (NREM 1 and NREM 2), less number of arousals, less apnoeic and hypopnea events during sleep. Furthermore, they revealed SWS and REM sleep rebound (increase in the percentage of SWS and REM sleep) and improved oxygen saturation during sleep (Heinzer et al., 2001; McArdle & Douglas, 2001; Morisson et al., 2001; Parrino et al., 2005; Verma et al., 2001). The normalization of sleep architecture and respiratory parameters during sleep leads to reduced sleepiness during in awake state (McDaid et al., 2009; Montserrat et al., 2001; Patel, White, Malhotra, Stanchina & Ayas, 2003).

The studies on treatment relating to the improvement of cognitive functioning in sleep apnea patients show inconsistent results. Some studies did not reveal post-training improvement in cognitive functions after short- (1 or 2 week or 1 month) CPAP treatment (Barbe et al., 2001; Bardwell, Ancoli-Israel, Berry & Dimsdale, 2001; Lim et al., 2007; Monasterio et al., 2001). In contrast, other studies found post-treatment improvement, but often this improvement was only partial, even after long-term CPAP therapy. These studies observed significant improvement in attention, visuospatial learning and motor performance after a 15-day-long CPAP treatment (Ferini-Strambi et al., 2003), in mental flexibility, information processing and visual abilities after a month (Engleman et al., 1997; Engleman et al., 1999), in verbal fluency and vigilance after two months of CPAP treatment (Barnes et al., 2002).

Few studies examined the potential reversibility of cognitive impairment after long-term CPAP therapy. These studies demonstrated significant improvement after three months in

attention (Munoz, Mayolaras, Barbé, Pericas & Agusti, 2000), concentration, verbal-, visual- and spatial memory (Borak et al., 1996; Lojander et al., 1999), but did not find any further improvement after one year.

Some studies attempt to identify a dose-response relationship between CPAP use and clinical outcomes measures. These studies have suggested that improvement in adherence to CPAP treatment may also be related to improvement in clinical outcomes, thereby supporting a dose-response relationship. These findings highlight the importance of the regular CPAP utilization both in the case of short- and long-term therapy (Campos-Rodriguez et al., 2005; Weaver, 2003; Zimmerman, Arnedt, Stanchina, Millman & Aloia, 2006).

Studies designed to assess the effect of short- and long-term CPAP therapy on mood in OSA patients which focused particularly on depression showed mixed results. Most of the studies identified improvement in depression after short- or long-term CPAP treatment (Canessa et al., 2010; Derderian, Bridenbaugh & Rajagopal, 1988; Jokic et al., 1998). However others did not reveal changes on affective impairment either after short- or long term CPAP treatment (Barbé et al., 2001; Bardwell et al., 2002; Munoz et al., 2000). In addition, Borak et al. (1996) demonstrated that CPAP treatment results in a significant early improvement in cognitive functions, but not in emotional status.

Taken together, studies which exam the effect of short- and long-term CPAP treatment on mood and cognitive functions found controversial results. The majority of these studies revealed partial reversibility in cognitive functioning and affective disorders after short- and long-term CPAP therapy. The effectiveness of CPAP and BiPAP treatment depends on the severity of OSA, the duration of treatment and the regular CPAP/BiPAP utilization. Further investigations are necessary to clarify whether the cognitive and affective dysfunction that might be caused by hypoxia and/or sleep deprivation is irreversible in the long-term.

Aim of the studies

Based on the aforementioned literature, the effect of sleep disorder on memory functions are under-researched and controversial both in children and adults. Thus, the lack of empirical studies and the controversial results motivated our experiments. 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.

Methods

Participants

Twenty children participated in Experiment I. Clinical characteristics of SDB patients and healthy subjects are listed in Table 1. The SDB was diagnosed by a board-certified sleep physician. The SDB group consisted of ten children with SDB (average age: 8.8 years, SD: 1.68; average education: 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 (Kennedy et al., 2004; Montgomery-Downs et al., 2005), the main difference between the groups is the Snoring Index ($t(9) = 2.87, p < 0.01; 0.1$ 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. 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. Informed written parental consent and verbal assent of the children were provided and participants did not receive financial compensation for their participation.

	Control (n=10)	SDB (n=10)	t(df)	p-value
Age yrs	9.3 (SD: 2.45)	8.8 (SD: 1.68)	-0.531(18)	0.602
Sex female/male n	3/7	5/5		
Education yrs	3.3 (SD: 2.54)	2.1 (SD:1.66)	-1.25(18)	0,22
BMI kg/m ²	16.64 (SD: 3.14)	15.77 (SD: 3.03)	-0.629 (18)	0.53
AHI events/hour	0.14 (SD: 0.22)	1.96 (SD: 2.81)	2.037 (9.11)	0.07**
Snore Index	0.1 (SD: 0.06)	11.00 (SD: 11.97)	2.87 (9)	0.01**
events/hour				
TST min.	464.11 (SD: 25.15)	473.1 (SD: 11.09)	0.988(10.7)	0.34
Letter fluency	8.4 (SD: 4.59)	5.6 (SD: 3.56)	-1.52(18)	0.14
Semantic fluency	14.2 (SD: 4.93)	13.5 (SD: 4.67)	-0.32(18)	0.74

Table 1: Data are presented mean and standard deviation or %, unless otherwise stated. **BMI:** body mass index kg/m²; **AHI:** Apnoe-Hypopnoe Index: apnetic and hypopnetic events per hour of sleep; **Snore Index:** snoring events per hour; **TST:** total sleep time (p<0.05**).

Tasks

Sequential learning task - Alternating Serial Reaction Time (ASRT)

We used a modified version of the original ASRT task in order to assess non-declarative /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) was repeated ten times. Following Nemeth et al. (2010), stimuli were presented 120-ms following the previous response. As one block took about 1.5 minutes, the session took approximately 25-30 minutes. 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 sec 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 4 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, where numbers represent the four places on the screen, and r represents an event randomly selected from the four possible places), 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 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 (Nemeth et al., 2010; Howard & Howard, 1997; Song et al., 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 compared to the low-frequency triplets (also known as non-adjacent 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 & Howard, 1997; Howard et al., 2004; 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.

Story recall - “The War of the Ghosts” Test

Declarative memory performance was measured by “The War of the Ghosts” test (Bartlett, 1932). This is a story recall test, which is widely used to measure episodic memory performance (Andreano & Cahill, 2006; Andreano & Cahill, 2008; 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 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, etc. 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 analyzes 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 & Howard, 1997; Howard et al., 2004). By eliminating them, we attempt to ensure that any high- versus low-frequency differences are due to learning and not to pre-existing tendencies.

Results

Accuracy analysis in the ASRT task

A mixed design ANOVA was conducted on the 5 epochs of the data shown in Figure 1a, 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 x GROUP interaction: $F(1,18) = .02$, $\eta_p^2 = .002$, $p = .87$). 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 x GROUP interaction: $F(4,72) = .45$, $\eta_p^2 = .02$, $p = .58$). The TRIPLET x EPOCH and TRIPLET x EPOCH x 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: $F(1,18) = .66$, $\eta_p^2 = .04$, $p = .42$), reflecting that 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 5 epochs of the data shown in Figure 1c, 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 x GROUP interaction: $F(1,18) = .01$, $\eta_p^2 = .001$, $p = .92$). 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 x GROUP interaction: $F(4,72) = .31$, $\eta_p^2 = .02$, $p = .66$). The TRIPLET x EPOCH and TRIPLET x EPOCH x GROUP interactions were not significant ($F(4,72) = 2.07$, $\eta_p^2 = .10$, $p = .14$; $F(4,72) = .16$, $\eta_p^2 = .009$, $p = .87$; 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: $F(1,18) = 1.09$, $\eta_p^2 = .06$, $p = .31$).

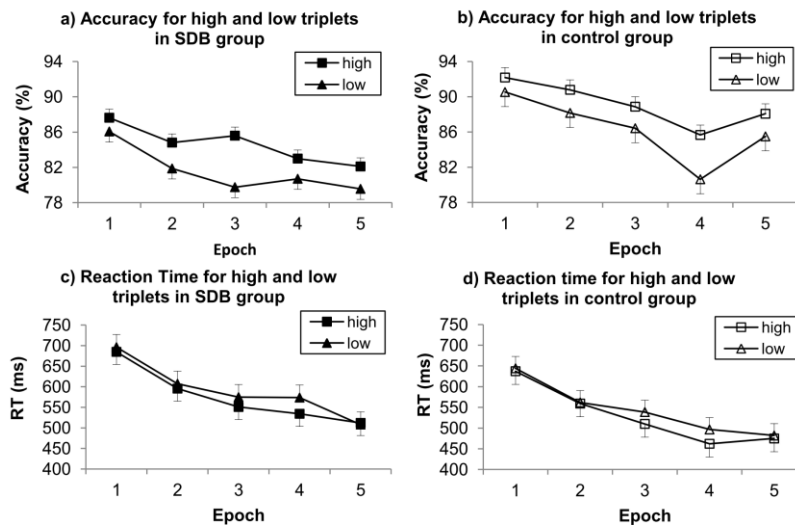


Figure 1. Results of accuracy for high and low triplets in SDB (a) and control groups (b): Both groups showed significant sequence-specific learning, such that accuracy was greater on high than on low frequency triplets. There was a trend in general skill learning for accuracy to decrease across epochs 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 for high and low frequency triplets in SDB (c) and control groups (d) are also plotted: Both groups demonstrated significant sequence-specific and general skill learning, such that RT was faster on high than 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).

“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 ($t(9) = 11.00, p < .001$ for the SDB group and $t(9) = 12.51, p < .001$ for the control group). Nevertheless, the declarative memory performance of the SDB group was significantly lower (7.7 (SD: 2.21) vs.14.7 (SD: 3.71) compared to the control group ($t(18) = -5.12, p < .001$, Cohen’s $d = 2.36$; Figure 2).

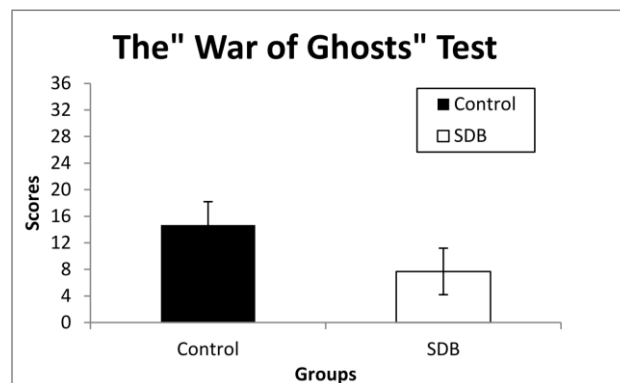


Figure 2. Declarative memory performance in SDB and control groups: The declarative memory performance of the SDB group was significantly lower compared to the control group. The dependent variable was the number of correctly recalled sentences. Error bars indicate SEM.

Study II.

Methods

Participants

Thirty-two children participated in the experiment. Breathing events during sleep, Body Mass Index (BMI) and working memory (WM) measures of the SDB patients and healthy participants are listed in Table 2. All participants underwent an overnight polygraphy, which was performed with the Somnomedics Somnoscreen plus device (Randersacker, Germany) at the Sleep Disorders Laboratory of Heim Pál Children’s Hospital, Budapest, Hungary.

Patients who met the International Classification of Sleep Disorders criteria's (American Academy of Sleep Medicine, 2001) for SDB were included in the study. SDB was diagnosed by a board-certified sleep physician. The SDB group consisted of sixteen children with SDB (average age: 8.56 years [min: 6 to max: 11 years], SD: 2.31; 6 females/10 males) six of them with OSA and ten of them with primary snoring. The Apnea/Hypopnea (AHI) index of the OSA patients ($M = 17.32$, $SD = 30.54$, range 2–79) was significantly higher (all p 's < 0.01) than that of the snoring patients ($M = 0.11$, $SD = 0.19$, range 0–1) as well as the controls ($M = 0.11$, $SD = 0.20$, range 0–1). Similarly, the snore index of the snoring patients ($M = 55.10$, $SD = 54.95$, range 6–155) was significantly higher (all p 's < 0.03) than that of the OSA patients ($M = 16.67$, $SD = 28.52$, range 0–73) as well as the controls ($M = 0.13$, $SD = 0.34$, range 0–1). According to the literature, the neurobehavioral deficits is associated with snoring in children are similar to those found in children with OSA (Gozal and O'Brien, 2004; O'Brien et al., 2004). Therefore, we compared the performance of the SDB group to that of controls and did not intend to examine the OSA and snoring subgroups separately. All SDB patients were untreated prior to and during the experimental night in the sleep laboratory. The control group consisted of sixteen healthy participants (average age: 8.75 years, SD: 1.44 [min: 6 to max: 15 years]; 8 females/8 males). The control and the patient groups were matched by age ($t(30) = 0.28$, $p = 0.78$) and gender ($\chi^2 = 0.51$, $p = 0.48$) and parental education (mother education: $t(12.54) < 0.001$, $p > 0.99$; father education $t(23) = 0.61$, $p = 0.55$). 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 any financial compensation for their participation. Ethics approval was obtained by the Ethics Committee at Heim Pal Children's Hospital, Budapest.

	Control (n=16)	SDB (n=16)	t(df)	p-value
Snore Index events/hour	0.13 (0.34)	40.69 (49.52)	-3.28 (15.001)	0.005**
AHI event/hour	0.11 (0.20)	6.56 (19.62)	-1.31 (15.003)	0.21
Max. Desaturation (%)	92.31 (4.13)	90.56 (7.75)	0.80 (30)	0.43
Desaturation Index (%)	0.56 (0.89)	11.25 (26.76)	-1.60 (15.003)	0.13
BMI kg/m ²	15.19 (1.22)	19.25 (5.17)	-3.06 (16.67)	0.01*
Counting Span	2.88 (0.72)	2.48 (0.55)	1.74 (30)	0.09⁺
Listening Span	2.40 (0.75)	2.16 (1.09)	0.72 (30)	0.48
Digit Span	4.81 (0.65)	4.50 (0.89)	1.13 (30)	0.27

Table 2: Snore Index: snoring events per hour; **AHI:** Apnea-Hypopnea Index: apnetic and hypopnetic events per hour of sleep; **Max. Desaturation:** the ratio of oxyhemoglobin to the total concentration of hemoglobin present in the blood; **Desaturation Index:** number of time/hour of sleep that the blood's oxygen level drops by 3% or more for the baseline; **BMI:** Body Mass Index kg/m². **Listening Span Task:** a working memory (WM)

task in which the participants are required to listen to increasingly longer sequences of sentences and to recall the final word of all the sentences in each sequence in serial order (Daneman & Blennerhassett, 1984). **Counting Span Task:** a WM task in which participants are required to count a growing number of colored dots on the computer screen and remember the number of the dots of each sequence (Case et al., 1982; * $p < 0.05$, ** $p < 0.01$, + $p < 0.10$).

Tasks

Sequential learning task - Alternating Serial Reaction Time (ASRT) Task

We used the same ASRT task as in the **Study I**. In Session 1 (Learning Phase) consisted of 25 blocks with 85 key presses in each block. In Session 2 (Testing Phase) consisted of 5 blocks; the number of key presses and the RSI were the same as in Session 1.

Story recall - “The War of the Ghosts” Test

We used the same story recall test as in **Study I**. In Session 1 (Learning Phase) children are asked to listen and repeat the story after immediately and after a determinate interval. In Session 2 children had to remember the story what listened in Session 1. Based on the standardized scoring, each sentence is allocated 1 point for the verbatim recalled sentences and 0.5 points for partly correct responses (the gist of the sentences) (Bartlett 1932).

Procedure

There were two sessions in the experiment. The declarative and non-declarative performance was assessed at 7–9 PM prior to sleep (Learning Phase/Session 1) and 7–9 AM after sleep (Testing Phase/Session 2), thus the average interval between the Learning and Testing Phase was 12 h. The order of the administration of declarative and non-declarative tasks was counterbalanced in order to minimize the interference between declarative and non-declarative tasks (see Brown and Robertson, 2007).

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, etc. 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.

Results

Accuracy analysis in the ASRT task

Online learning during Session 1 (Learning Phase)

A mixed design ANOVA was conducted on the 5 epochs of the data shown in Figure 3 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: $F(1, 30) = 61.26$, $\eta_p^2 = 0.67$, $p < 0.001$), such that accuracy was greater on high- than on low-frequency triplets. SDB and control groups showed no differences in sequence-specific learning (TRIPLET x GROUP interaction: $F(1, 30) = 0.29$, $\eta_p^2 = 0.01$, $p = 0.59$).

The main effect of EPOCH did not reach significance ($F(4, 120) = 2.58$, $\eta_p^2 = 0.07$, $p = 0.06$), although accuracy decreased across epochs on a trend level. SDB and control groups performed at the same level (EPOCH x GROUP interaction: $F(4, 120) = 1.29$, $\eta_p^2 = 0.04$, $p = 0.28$).

The TRIPLET x EPOCH interaction was significant ($F(4, 120) = 3.37$, $\eta_p^2 = 0.10$, $p = 0.01$), but there were no significant differences between the groups (indicating by the TRIPLET x EPOCH x GROUP interaction: $F(4, 120) = 0.41$, $\eta_p^2 = 0.01$, $p = 0.79$; respectively), demonstrating that the pattern of learning was similar in the groups. The main effect of GROUP did not reach significance ($F(1, 30) = 3.91$, $\eta_p^2 = 0.11$, $p = 0.06$), although the SDB group had lower accuracy on a trend level (SDB group: 88.6% vs, control group: 91.8%)

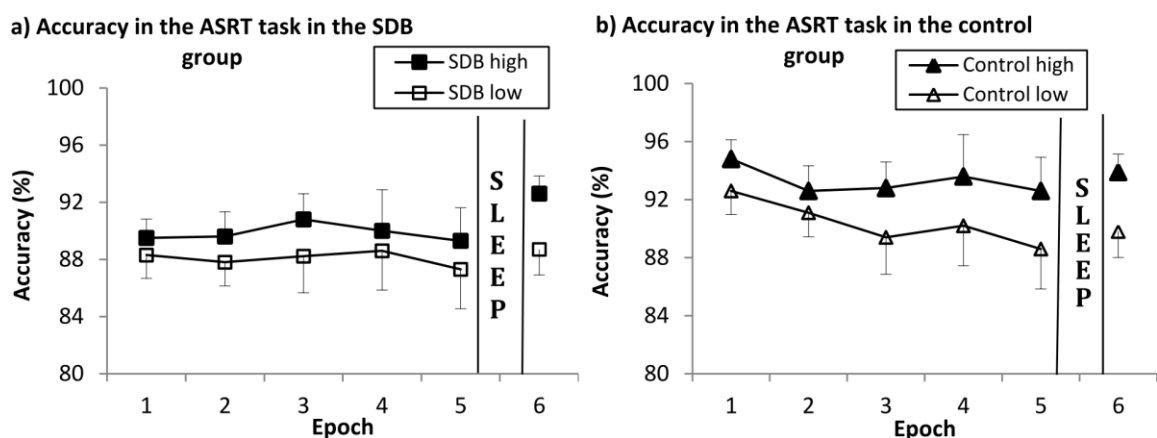


Figure 3. Results of sequence-specific and general skill learning in SDB (a) and control group (b) in Session 1 (Epoch 1-5) and Session 2 (Epoch 6) on accuracy measures. Both groups showed significant sequence-specific

and general skill learning. There were no differences in learning and in offline changes between the groups; the pattern of learning was similar in the SDB and control groups. Error bars indicate SEM.

Offline consolidation of sequence-specific and general skill learning

To investigate the offline changes of sequence-specific and general skill learning we compared the accuracy from the last epoch of Session 1 (Epoch 5) and the epoch of Session 2 (Epoch 6) in both groups. These variables were submitted to a mixed design ANOVA with TRIPLET (2: high- vs. low-frequency) and EPOCH (2: last epoch of Session 1 and epoch of Session 2) as within-subject factors, and GROUP (SDB vs. control) as a between-subject factor. The data is shown in Figure 3.

There was significant sequence-specific learning (indicating by the main effect of TRIPLET) ($F(1, 30) = 95.40$, $\eta_p^2 = 0.76$, $p < 0.001$), such that accuracy was greater on high- than on low-frequency triplets. It was similar in the SDB and control groups (indicated by the non-significant TRIPLET x GROUP interaction: $F(1, 30) = 0.04$, $\eta_p^2 = 0.002$, $p = 0.82$).

There was general skill learning (indicating by the main effect of EPOCH) ($F(1, 30) = 13.40$, $\eta_p^2 = 0.30$, $p = 0.01$), thus accuracy increased from evening to morning. SDB and control groups performed at the same level (EPOCH x GROUP interaction: $F(1, 30) = 3.26$, $\eta_p^2 = 0.09$, $p = 0.08$).

The TRIPLET x EPOCH and TRIPLET x EPOCH x GROUP interactions were not significant ($F(1, 30) = 0.20$, $\eta_p^2 = 0.01$, $p = 0.65$; $F(1, 30) = 0.28$, $\eta_p^2 = 0.01$, $p = 0.59$; respectively), indicating that the pattern of learning was similar in the groups. The main effect of GROUP was not significant ($F(1, 30) = 1.31$, $\eta_p^2 = 0.04$, $p = 0.26$), reflecting that all groups responded with similar accuracy rates (SDB group: 88.8%, control group: 91.2%).

Reaction time analysis in the ASRT task

Online learning during Session 1 (Learning Phase)

To investigate learning during Session 1, a mixed design ANOVA was conducted on the first 5 epochs of the data shown in Figure 4, with TRIPLET (2: high- vs. low-frequency) and EPOCH (5: 1-5) as within-subject factors, and GROUP (SDB vs. control) as a between-subject factor.

Our data revealed significant sequence-specific learning (indicated by the significant main effect of TRIPLET: $F(1, 30) = 64.33$, $\eta_p^2 = 0.68$, $p < 0.001$), such that RTs were faster on high- than on low-frequency triplets. SDB and control groups showed no differences in

sequence-specific learning (TRIPLET x GROUP interaction: $F(1, 30) = 0.59$, $\eta_p^2 = 0.04$, $p = 0.44$).

There was also significant general skill learning (shown by the significant main effect of EPOCH: $F(4, 120) = 54.80$, $\eta_p^2 = 0.64$, $p < 0.001$), such that RTs decreased across epochs. SDB and control groups performed at the same level (EPOCH x GROUP interaction: $F(4, 120) = 0.95$, $\eta_p^2 = 0.03$, $p = 0.38$).

The TRIPLET x EPOCH interaction was significant ($F(4, 120) = 5.26$, $\eta_p^2 = 0.14$, $p = 0.003$), suggesting that sequence-specific knowledge increased during practice. The TRIPLET x EPOCH x GROUP interaction was not significant ($F(4, 120) = 0.49$, $\eta_p^2 = 0.013$, $p = 0.67$), indicating that the pattern of learning was similar in the groups. In overall RT both group performed at the same level (main effect of GROUP: $F(1, 30) = 1.37$, $\eta_p^2 = 0.04$, $p = 0.25$).

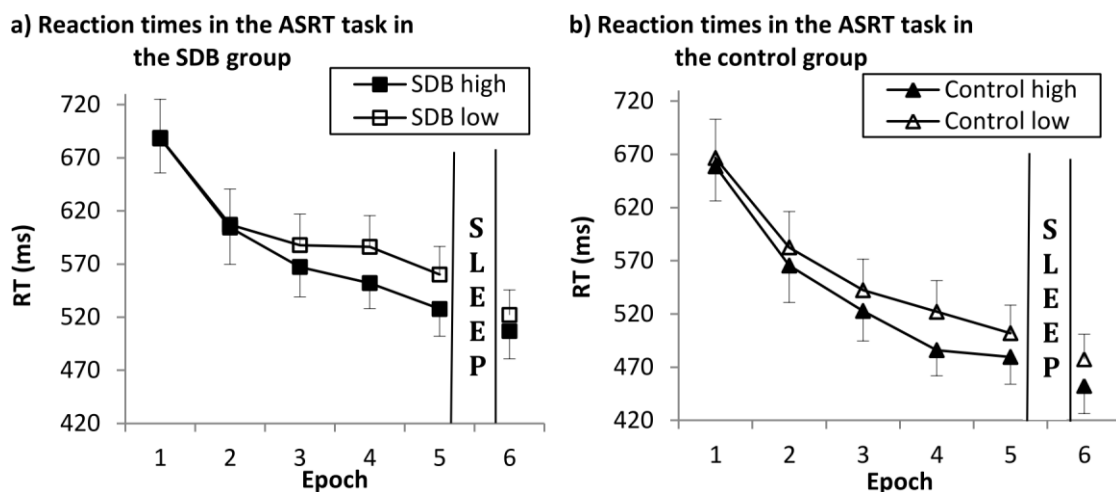


Figure 4. Results of sequence-specific and general skill learning in SDB (a) and control (b) group in Session 1 (Epoch 1-5) and Session 2 (Epoch 6) on reaction time measures. Both groups showed significant sequence-specific and general skill learning. There were no differences in learning and in offline changes between the groups; the pattern of learning was similar in the SDB and control groups. Error bars indicate SEM.

Offline consolidation of sequence-specific and general skill learning

To investigate the offline changes of sequence-specific and general skill learning we compared the RTs from the last epoch of Session 1 (Epoch 5) and the epoch of Session 2 (Epoch 6) in both groups. These variables were submitted to a mixed design ANOVA with TRIPLET (2: high- vs. low-frequency) and EPOCH (2: last epoch of Session 1 and epoch of Session 2) as within-subject factors, and GROUP (SDB vs. control) as a between-subject factor. The data is shown on Figure 4.

There was significant sequence-specific learning (indicating by the main effect of TRIPLET) ($F(1, 30) = 125.76$, $\eta_p^2 = 0.80$, $p < 0.001$), thus RTs were faster on high- than low-frequency triplets when analyzing the two epochs together. The groups did not differ in overall sequence-specific learning (indicated by the non-significant TRIPLET x GROUP interaction: $F(1, 30) = 0.42$, $\eta_p^2 = 0.01$, $p = 0.51$).

There was significant general skill learning during the offline period (demonstrated by the main effect of EPOCH: $F(1, 30) = 20.71$, $\eta_p^2 = 0.40$, $p < 0.001$), such that RTs were faster in the morning compared to the evening. The SDB and control groups showed similar level of offline general skill learning (EPOCH x GROUP interaction: $F(1, 30) = 0.24$, $\eta_p^2 = 0.01$, $p = 0.62$).

The TRIPLET x EPOCH and the TRIPLET x EPOCH x GROUP interactions were not significant ($F(1, 30) = 0.84$, $\eta_p^2 = 0.02$, $p = 0.36$; $F(1, 30) = 2.18$, $\eta_p^2 = 0.06$, $p = 0.15$, respectively), indicating that the SDB and the control group demonstrated no differences in the pattern of offline changes. There were no significant differences in the overall RTs between the SDB and control groups (main effect of GROUP: $F(1, 30) = 2.54$, $\eta_p^2 = 0.07$, $p = 0.12$).

Story recall test

We conducted a mixed design ANOVA with SESSION (1-2) as a within-subject factor and GROUP (SDB vs. control) as a between-subject factor to assess offline changes in declarative memory performance. The main effect of GROUP was significant ($F(1, 29) = 6.155$, $\eta_p^2 = 0.175$, $p = 0.019$), indicating weaker story recall performance in the SDB compared to the controls (6.267 vs. 10.406, respectively). This weaker performance of the SDB group compared to the control group was evident both in Session 1 (6.87 vs. 10.38; $p = 0.03$) and in Session 2 (5.67 vs. 10.44; $p = 0.01$) (Figure 5). The main effect of SESSION failed to reach significance ($F(1, 29) = 2.05$, $\eta_p^2 = 0.06$, $p = 0.16$), suggesting no change in the performance during the offline period. Similarly, the SESSION x GROUP interaction was not significant either ($F(1, 29) = 2.53$, $\eta_p^2 = 0.08$, $p = 0.12$), suggesting no differences in offline changes between the SDB and control groups.

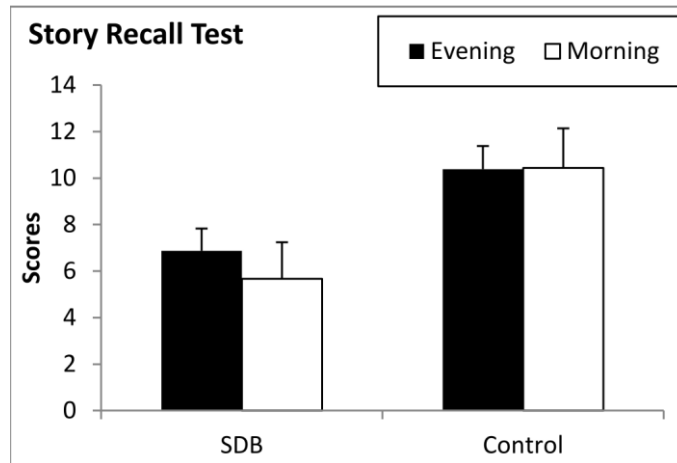


Figure 5. Declarative memory performance in the evening and in the morning in the SDB and control groups. The dependent variable was the number of correctly recalled sentences. The overall declarative memory performance of the SDB group was significantly lower compared to the control group, but there were no offline changes in the memory performance in either group. Error bars indicate SEM.

Study III.

Methods

Participants

Twenty untreated participants were included in the OSA group (average age: 52.70, SD: 9.60; average education: 11.95, SD: 2.62, 3 female/17 male). OSA was diagnosed by a board-certified sleep-physician based on a full night of clinical polysomnography. The mean Apnea-Hypopnea Index (AHI) was 50.76 event/hour, SD: 22.20 (Range: 21.10-117.30). The pathological level of AHI defined as 15 or more per hour (Banno & Kryger, 2007). The mean of Respiratory Disturbance Index (RDI) in total sleep time was 60.97 event/hour, SD: 16.76 (Range: 33.10-86.80). RDI was calculated as the number of respiratory events (respiratory effort-related arousal (RERA) + apneas + hypopneas) per hour of sleep. The Pathological level of RDI defined as 10 or more per hour (Peker, Hedner, Kraiczi & Loth 2000). The mean of the daytime sleepiness measured by the Epworth Sleepiness Scale was 10.00, SD: 4.44 (Range: 2-18). Aside from OSA, participants did not suffer from any developmental, psychiatric or neurological disorder as established in a full neurological exam by a board certified neurologist.

The control group consisted of twenty healthy subjects and were matched by age, education, and sex (average age: 52.40, SD: 15.04, average education: 12.65, SD: 3.56, 5 female/15 male). The control participants did not suffer from any developmental, psychiatric

or neurological disorders and did not have sleeping disorders. All subjects provided signed informed consent agreements and received no financial compensation for their participation.

Tasks

Sequential learning task - Alternating Serial Reaction Time (ASRT) Task

We used the same ASRT task in the Experiment I. and Experiment II. The task consisted of one practice block with random stimuli and 20 blocks with the alternating pattern described above. To explore how much explicit knowledge participants acquired about the task, we administered a short questionnaire (the same as Nemeth et al., 2010; Song et al., 2007) after the task. This questionnaire included increasingly specific questions such as “Have you noticed anything special regarding the task? Have you noticed some regularity in the sequence of stimuli?” The experimenter rated subjects’ answers on a 5-item scale, where 1 was “Nothing noticed” and 5 was “Total awareness”. None of the subjects in either the apnea or control group reported noticing the sequence in the task.

Working memory task – Listening Span Task

The working memory performance was measured by the Listening Span Task (Daneman and Blennerhassett, 1984; Janacsek, Tánczos, Mészáros & Nemeth, 2009). In this test, subjects are required to listen to increasingly longer sequences of sentences and to recall the final word of all the sentences in each sequence in serial order. A subject's working memory capacity is defined as the longest sequence length at which they are able to recall the final words.

Procedure

We administered the Listening Span Task and ASRT task in one session between 6 and 9 PM both in OSA and 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 contains blocks 1-5, the second epoch contains blocks 6-10, etc (Nemeth et al., 2010; Song et al., 2007). Subjects’ accuracy remained very high throughout the test (average over 96% for both groups), and so we focus on RT for the analyses reported.

We calculated medians for correct responses only, separately for high- and low-frequency triplets and for each participant.

Results

Reaction time analysis in the ASRT task

A mixed design ANOVA was conducted on the 4 epochs of the data shown in Figure 6 with (TRIPLET: high vs. low) and (EPOCH: 1-4) as within-subjects factors, and GROUP (OSA vs. control) as between-subjects factors.

There was significant sequence-specific learning (indicated by the significant main effect of TRIPLET: $F(1,38) = 11.18$, $\eta_p^2 = 0.23$, $p = 0.002$) such that RT was faster on high than low frequency triplets. OSA and control groups showed no differences in sequence-specific learning (TRIPLET x GROUP interaction: $F(1,38) = 1.21$, $\eta_p^2 = 0.03$, $p = 0.28$).

There was also general skill learning (shown by the significant main effect of EPOCH: $F(3,114) = 31.07$, $\eta_p^2 = 0.45$, $p < 0.001$), such that RT decreased across epochs. OSA and control groups performed at the same level (EPOCH x GROUP interaction: $F(3,114) = 0.05$, $\eta_p^2 = 0.001$, $p = 0.98$).

The TRIPLET x EPOCH and TRIPLET x EPOCH x GROUP interactions were not significant ($F(3,114) = 1.60$, $\eta_p^2 = 0.04$, $p = 0.19$; $F(3,114) = 0.78$, $\eta_p^2 = 0.02$, $p = 0.50$; respectively), indicating that the pattern of learning was similar in the groups. In the general reaction time the OSA group did not differ significantly from the control group, we found only a weak trend (main effect of GROUP: $F(1,38) = 2.97$, $\eta_p^2 = 0.07$, $p = 0.093$). Because of this slight difference in general reaction time, we reanalyzed the data using z-scores and found the same results as in the original analysis with no differences between the groups regarding sequence-specific and general skill learning (TRIPLET x GROUP interaction: $F(1,38) = 0.09$, $p = 0.77$; EPOCH x GROUP interaction: $F(3,114) = 0.20$, $p = 0.89$; TRIPLET x EPOCH x GROUP interaction: $F(3,114) = 0.92$, $p = 0.92$).

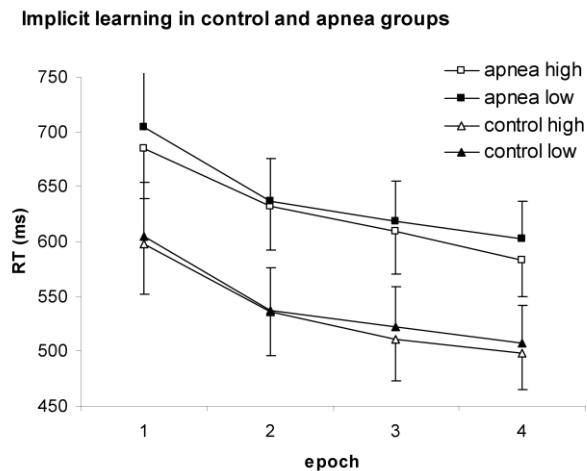


Figure 6. Implicit sequence learning in control and sleep apnea group. Both groups showed general skill learning as well as sequence-specific learning. There were no group differences. Error bars indicate standard error of mean.

Listening Span Task

The performance in the Listening span task was analyzed by independent samples t-test. The working memory span of the OSA group was significantly lower (2.55 vs. 3.31) compared to the control group ($t(38) = -4.05, p < 0.001$; Figure 7).

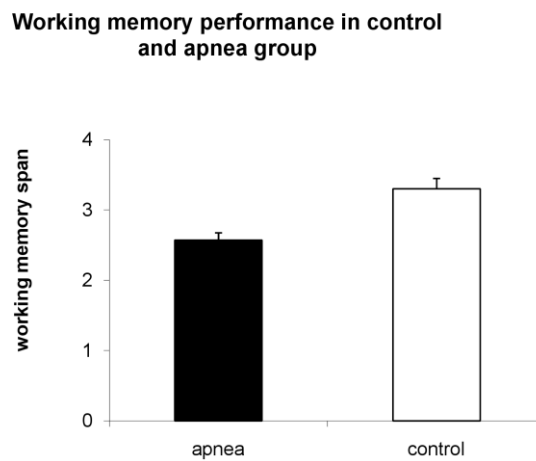


Figure 7. Working memory performance in control and sleep apnea group. The working memory span of the sleep apnea group was significantly lower compared to the control group. Error bars indicate standard error of mean.

Study IV.

Methods

Participants

Seventeen newly diagnosed, untreated patients with OSA participated in the experiment (average age: 52.41 years, SD: 9.67; average education: 12.65 years, SD: 2.18; 2 females/15 males). OSA was diagnosed by a board-certified sleep-physician based on a full night of clinical polysomnography. The mean Apnea-Hypopnea Index (AHI) was 53.05 events/hour (SD: 23.26 (Range: 21.1-117.3)). Pathological level of AHI was defined as 15 or more per hour (Banno & Kryger, 2007). The mean total sleep time (TST) was 330.52 min (SD: 48.65). Aside from OSA, participants did not suffer from any developmental, psychiatric or neurological disorders as established in a full neurological exam by a board-certified neurologist.

The control group consisted of seventeen healthy participants and was matched by age (average age: 54.24 years, SD: 7.29) and by working memory performance. Working memory capacity was assessed by two widely-used neuropsychological tests: the Backward Digit Span Task (BDST) (Conway et al., 2005; Richardson, 2007) and Listening Span Task (LST) (Janacsek et al., 2009). There were no significant differences between the two groups in these tasks (BDST: $t(32) = 1.116$, $p = 0.27$, LST: $t(32) = 0.170$, $p = 0.87$). These criteria were included to eliminate the effect of working memory, as previous studies in healthy participants revealed a relationship between working memory and implicit sequence learning (Bo et al., 2011; Frensch & Miner, 1994). However there is also evidence that the two systems are independent of each other (Kaufman et al., 2010; Unsworth & Engle, 2005) (for review see Janacsek & Nemeth, 2013). Control participants did not suffer from any developmental, psychiatric or neurological disorders and did not have sleeping disorders. All participants provided signed informed consent and received no financial compensation for their participation.

Task

Sequential learning task - Alternating Serial Reaction Time (ASRT) Task

We used the same ASRT task as in Experiment I., Experiment II. and Experiment III. During Session 1 (Learning Phase), the ASRT task consisted of 25 blocks, while Session 2 (Testing Phase) consisted of only 5 blocks of the same type as in Session 1. The repeating sequence was identical between Session 1 and Session 2 for each participant. To explore how

much explicit knowledge subjects acquired about the task, we administrated a short questionnaire as in the previous experiments. None of the participants reported noticing the repeating of the stimulus locations.

Procedure

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 and 8 PM prior to sleep (Learning Phase) and between 7 and 8 AM after sleep (Testing Phase), thus the average interval between the Learning and Testing Phase was 12 hours. Between the two sessions AHI was measured in a full night of polysomnography in SomnoCenter's sleep lab (Szeged, Hungary). During the data collection, subjects' caffeine and nicotine intake were restricted.

Statistical Analysis

To facilitate data processing, stimulus blocks were organized into larger clusters (called: epochs); where the first epoch contained blocks 1-5, the second epoch blocks 6-10, etc. (Nemeth et al., 2010; Song et al., 2007). Consequently, Session 1 consisted of 5 epochs, whereas Session 2 consisted 1 epoch. The accuracy of responses remained very high throughout the test (average over 97% for all groups), resulting ceiling effect. Therefore, we analyzed the median reaction time (RT) for correct responses only, calculated separately for high- and low-frequency triplets and for each epoch.

Results

Online learning during Session 1 (Learning Phase)

To investigate learning during Session 1, a mixed design ANOVA was conducted on the first 5 epochs of the data shown in Figure 8A, with TRIPLET (2: high- vs. low-frequency) and EPOCH (5: 1-5) as within-subject factors, and GROUP (OSA vs. control) as a between-subject factor. All significant results are reported together with the η_p^2 effect size and Greenhouse Geisser ϵ correction factors where applicable. Post hoc analyzes were conducted by Fisher's LSD pairwise comparisons.

There was significant sequence-specific learning (indicated by the significant main effect of TRIPLET: $F(1,32) = 15.58$, $\eta_p^2 = 0.32$, $p < .001$), such that RTs were faster on high-

than on low-frequency triplets. OSA and control groups showed no differences in sequence-specific learning (TRIPLET x GROUP interaction: $F(1,32) = 1.61$, $\eta_p^2 = 0.04$, $p = 0.21$).

There was also significant general skill learning (shown by the significant main effect of EPOCH: $F(4,128) = 28.62$, $\eta_p^2 = 0.47$, $p < 0.001$), such that RTs decreased across epochs. OSA and control groups performed at the same level (EPOCH x GROUP interaction: $F(4,128) = 2.21$, $\eta_p^2 = 0.06$, $p = 0.12$).

The TRIPLET x EPOCH and TRIPLET x EPOCH x GROUP interactions were not significant ($F(4,128) = 0.94$, $\eta_p^2 = 0.03$, $p = 0.42$; $F(4,128) = 0.48$, $\eta_p^2 = 0.01$, $p = 0.69$; respectively), indicating that the pattern of learning was similar in the groups. In the overall RT, the OSA group differed significantly from the control group, with slower RTs for the OSA group (main effect of GROUP: $F(1,32) = 4.95$, $\eta_p^2 = 0.13$, $p = 0.03$). To ensure that this difference in overall RTs did not influence learning measures, we also ran an ANOVA on normalized data (for each participant, the median RTs for high- and low-frequency triplets in each epoch were divided by the overall RT of the first epoch) and found the same results.

Consolidation of sequence-specific and general skill learning

To investigate the offline changes of sequence-specific and general skill learning we compared the RTs from the last epoch of Session 1 (Epoch 5) and the epoch of Session 2 (Epoch 6) in both groups. These variables were submitted to a mixed design ANOVA with TRIPLET (2: high- vs. low-frequency) and EPOCH (2: last epoch of Session 1 and epoch of Session 2) as within-subject factors, and GROUP (OSA vs. control) as a between-subject factor.

The main effect of TRIPLET was significant ($F(1,32) = 32.34$, $\eta_p^2 = 0.5$, $p < 0.001$), thus RTs were faster on high- than low-frequency triplets. It was similar in the OSA and control groups (indicated by the non-significant TRIPLET x GROUP interaction: $F(1,32) = 1.07$, $\eta_p^2 = 0.03$, $p = 0.31$).

The main effect of EPOCH did not reach significance ($F(1,32) = 2.34$, $\eta_p^2 = 0.07$, $p = 0.13$) but the EPOCH x GROUP interaction was significant ($F(1,32) = 9.32$, $\eta_p^2 = 0.22$, $p = 0.005$), suggesting that the OSA and control groups showed significant differences in the offline changes of general skills. The LSD post hoc test revealed that the OSA group showed no offline general skill improvement ($p = 0.29$) while the control group showed better

performance (faster RTs) at the beginning of Session 2 compared to the end of Session 1 ($p = 0.003$).

The sequence-specific knowledge did not change significantly during the offline period (TRIPLET x EPOCH interaction: $F(1,32) = 2.75$, $\eta_p^2 = 0.08$, $p = 0.11$). The OSA and control groups performed on a similar level (TRIPLET x EPOCH x GROUP interaction: $F(1,32) = 0.29$, $\eta_p^2 = 0.009$, $p = 0.59$). The offline changes of sequence-specific and general skill knowledge are shown on Figure 8B-C, respectively.

There were significant differences in the general RTs between the OSA and control groups, with slower RTs for the OSA group (main effect of GROUP: $F(1,32) = 6.27$, $\eta_p^2 = 0.16$, $p = 0.02$). ANOVA on normalized data revealed the same results, confirming that the significant difference in offline changes of general skills between the OSA and the control group was not due to general RT differences (EPOCH x GROUP interaction: $F(1,32) = 11.17$, $\eta_p^2 = 0.25$, $p = 0.002$).

To further confirm the ANOVA results we also analyzed individual differences of sequence-specific and general skill consolidation. In the case of offline sequence-specific changes, we counted the number of participants who exhibited higher sequence-specific learning in Epoch 6 than in Epoch 5 (thus, sequence-specific knowledge in Epoch 6 minus Epoch 5 was above zero, irrespectively of significance testing). A similar number of OSA and control participants (7/17 and 6/17, respectively) showed higher than zero difference in sequence-specific knowledge between Epoch 6 and Epoch 5. Consequently, the number of participants showing the opposite pattern (lower than zero difference between Epoch 6 and Epoch 5) was also similar in the two groups (10/17 and 11/17, respectively). Thus, there was no group difference in sequence-specific consolidation based on this analysis (chi-square(1) = 0.125, $p = 0.724$) which supports the ANOVA result. In contrast, in the case of general skill consolidation, more controls (14 out of 17) than OSA patients (8 out of 17) showed higher than zero difference in general RTs between Epoch 6 and Epoch 5, thus, they were generally faster in Epoch 6 compared to Epoch 5. This group difference in general skill consolidation was significant (chi-square (1) = 4.636, $p = 0.031$) similarly to the ANOVA result.

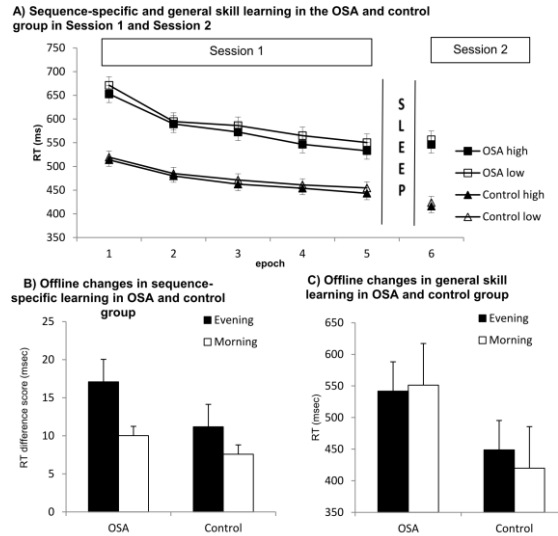


Figure 8. Results of sequence learning and consolidation in the OSA and control group. **A)** Results of sequence-specific and general skill learning in OSA and control group in Session 1 and Session 2: Although the OSA group was generally slower in Session 1, both groups showed significant sequence-specific and general skill learning. There were no differences in learning between the groups; the pattern of learning was similar in the OSA and control groups. **B)** Results of offline changes in sequence-specific learning in OSA and control group: The differences between the low and high-frequency triplets indicate sequence-specific learning. There was a decrease in sequence-specific knowledge, such that the learning index of the first epochs of Session 2 was significantly smaller compared to the last epochs of Session 1. There were no significant differences between the OSA and control groups. **C)** The results of offline changes in general skill learning: the differences in overall reaction time between the last epoch of Session 1 and the first epoch of Session 2 regardless of triplet type show general skill learning. There was a trend of improvement in general skill learning. The OSA group showed no offline general skill learning while the control group showed better performance (smaller RTs) at the beginning of Session 2 compared to the end of Session 1. Error bars indicate SEM.

Study V.

Methods

Participants

Twenty-four newly diagnosed and untreated patients with OSA participated in Experiment V. (average age: 53.21 years, SD: 12.11; average education: 12.17 years, SD: 2.20; 1 females/15 males). OSA was diagnosed by a board-certified sleep-physician based on a full night of clinical polysomnography. The mean apnea-hypopnea index (AHI) was 54.07 event/hour (SD: 23.26). Aside from OSA, participants did not suffer from any developmental, psychiatric or neurological disorders as established in a full neurological examination by a

board-certified neurologist. According to the apnoe-hypopnoe index, 16 of them were severe, 5 of them were moderate and 3 of them were with mild OSA. Sixteen of them have received BIPAP and 8 have received CPAP devices. All participants provided signed informed consent and received no financial compensation for their participation.

Tasks

Short-term verbal memory

Digit Span Task – the participants are presented with a series of digits and had to immediately repeat them back. The task started with three-element sequence and gradually increased in length up to nine-element sequence. We measured the number of the correct sequences and the longest sequence that the participants remembered. The length of the longest sequence a subject can remember is that subject's short-term memory span (Gathercole, Willis, Baddeley & Emslie, 1994; Szendi, Kiss, Racsomány, Pléh & Janka, 2005).

Non - Word Repetition Task – the participants are required to listen and recall to increasingly longer unmeaning words which are phonologically identical with the participant's native language. The task started with three words and gradually increased in length up to nine words. We measured the number of the correct words and the longest words that the participants remembered (Gathercole et al., 1994; Racsomány, Lukács, Németh & Pléh, 2005).

Complex working memory

Listening Span Task – participants are required to listen to increasingly longer sequences of sentences and to recall the final word of all the sentences in each sequence in serial order. A subject's working memory capacity is defined as the longest sequence length at which they are able to recall the final words (Daneman & Blennerhassett, 1984; Janacsek et al., 2009).

Backward Digit Span Task - the participants are presented with a series of digits and had to immediately repeat in reverse order. The task started with three-element sequence and gradually increased in length up to nine-element sequence. We measured the number of the correct sequences and the longest sequence that the participants remembered. The length of the longest sequence a subject can remember is that subject's short-term memory span (Gathercole et al., 1994; Szendi et al., 2005).

Short-term visual memory

Corsi Block-Tapping Task – the participants had to remember the right order of the blocks that get marked and then showed the same order. The task started with three numbers of blocks and gradually increased in length up to nine blocks. We measured the number of the correct sequences and the longest sequence remembered. The short-term visual memory span is the longest sequence that the participants can repeat back in correct order immediately after the presentation on 50% of all trial (Richardson, 2007; Szendi et al., 2005).

Executive functions

Letter and Semantic Fluency – the participants had to list as many words as possible with a beginning with the specified letter (letter fluency) or from specified category (semantic fluency) in 60 seconds (Tánczos, Janacsek & Németh, 2014/a; Tánczos et al., 2014/b). In our study, in the case of letter fluency we used “k” and “t” letters before treatment and “m” and “s” letters after treatment. A case of semantic fluency we used “animals” category before treatment and “food products” category after treatment. We measured the number of correct words, the perseverations and errors both in letter and semantic fluency tasks.

Short and long-term verbal and visual memory

Rivermead Behavioral Memory Task - is designed to predict everyday memory problems consisted of 11 subtests. We used story recall, remembering first-, and last name and pictures about objects immediate and delayed conditions (Kónya, Czigler, Racsmány, Takó & Tariska, 2000; Wilson, Cockburn & Baddeley, 1985).

Anxiety

State-Trait Anxiety Inventory – self-report questionnaire consist of 40 questions measuring state (anxiety level at the moment) and trait (anxiety level as a personal characteristic) anxiety. The participants had to decide how the sentences characterized them on a 4 point Likert-scale. The two subscales can be obtained in a total of 80 points (Sipos & Sipos, 1970; Spielberger, Gorsuch & Lushene, 1970).

Sleepiness

Epworth Sleepiness Scale – self-administered questionnaire where the participants had to rate the chances that they would doze off or fall asleep in eight different situations commonly

encountered in daily life. A total of 24 point can be achieved on the test. The pathological level of sleepiness defined as 10 point or more (John, 1991).

Procedure

There was 3 Session 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 polygraphy 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 and 8 PM in both cases. After the two and half month therapy, the average usage of PAP devices was 370 hour.

Statistical Analysis

We used independent sample t-test to evaluate the effect of two and half month PAP treatment and Pearson-correlation to assess the relationship between the cognitive functions, anxiety, sleep parameters and respiratory functions during sleep.

Results

Comparison between Session 1 and Session 2

Sleep structure and respiratory functions during sleep

In the titration night when the participants have already used the PAP devices we observed significant decreases in wakefulness during sleep (total wakefulness (TWK): $t(14) = 3.640, p = 0.003$) and reduction of NREM 1 ($t(14) = 3.659, p = 0.003$) compared to diagnostic night. Furthermore, we found significant increases in the amount of slow wave sleep (SWS) ($t(14) = -5.660, p < 0.001$) and REM sleep ($t(14) = -5.660, p < 0.001$), which led to increased total sleep time (TST) ($t(14) = -3.192, p = 0.007$). These changes in sleep parameters resulted increased sleep efficiency index ($t(14) = -3.478, p = 0.004$).

We observed significant improvement of respiratory functions during sleep indicating by the decreased respiratory disturbance index (RDI: ($t(15) = 7.220, p < 0.001$) and apnoe-hypopnoe index (AHI: ($t(22) = 6.687, p < 0.001$). In addition, the apnetic patients demonstrated improved saturation (indicating by the minimum SaO₂: $t(22) = -7.911, p < 0.001$, mean SaO₂: $t(22) = -2.353, p = 0.028$ and oxygen desaturation index (ODI): $t(22) = 15.311, p < 0.001$) in the titration night compared to diagnostic night.

Comparison between Session 1 and Session 3

Respiratory functions during sleep

After two and half month PAP treatment we used poligraphy, thus we observed the respiratory events during sleep. Based on poligraphy measurement, we found significant improvement in AHI index ($t(22) = 5.172, p < 0.001$) and saturation (indicated by the minimum SaO₂: $t(22) = -6.698, p < 0.001$, mean SaO₂: $t(22) = -3.869, p < 0.001$, ODI: $t(22) = 10.173, p < 0.001$) after two and half month CPAP/BIPAP therapy. Furthermore, we revealed significant improvement in level of subjective sleepiness measured by Epworth Sleepiness Scale (ESS) ($t(19) = 4.250, p < 0.001$) (see in Figure 9).

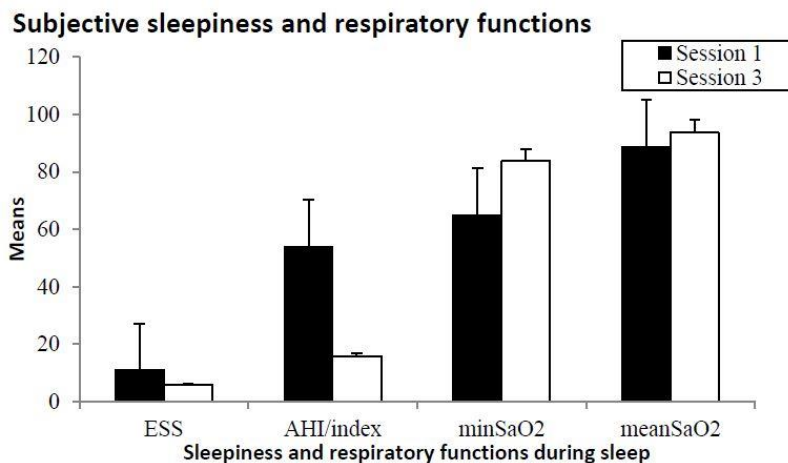


Figure 9. Results of sleepiness and respiratory functions before and after 2 and half month treatment: The OSA groups showed significant improvement in subjective sleepiness (ESS), apnetic/hypopnetic events (AHI/index) and saturation indicated by the minimum saturation (minSaO₂) and mean saturation (mean SaO₂). Error bars indicate SEM.

Cognitive functions and anxiety

After two and half month PAP treatment we found significant improvement in complex working memory measured by Backward Digit Span Task ($t(23) = -3.158, p = 0.004$) and Listening Span Task ($t(23) = -2.068, p = 0.050$). Furthermore, patients showed significant improvement in short- and long term verbal memory performance assessed by the immediate ($t(23) = -4.309, p < 0.001$) and delayed story recall ($t(23) = 3.715, p = 0.001$) in Rivermead Behavioral Memory Task (RBMT). In addition, we found a trend of improvement in immediate recognition performance of object pictures measured by RBMT ($t(23) = -1.813, p$

= 0.083). In contrast to these results, we revealed significant impairment in delayed condition of remembering of first and last name ($t(23) = 3.715, p = 0.003$). (Figure 10).

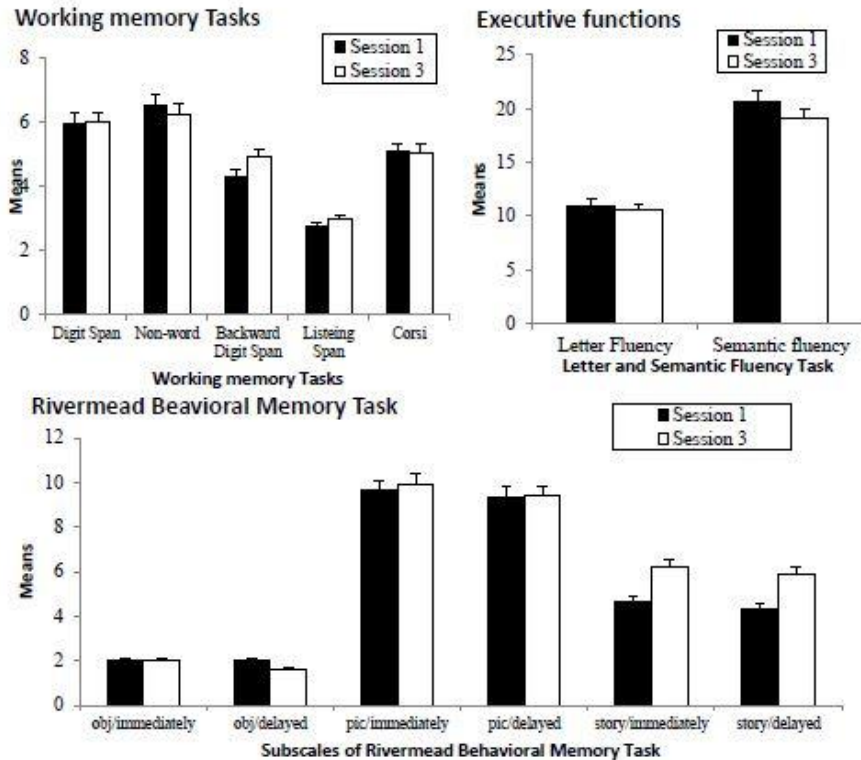


Figure 10. Results of cognitive functions before and after 2 and half month treatment: The OSA group demonstrated significant improvement in Backward Digit Span Task, Listening Span Task and immediate and delayed story recall in the Rivermead Behavioral Memory Task. We found a trend of improvement in immediate recognition performance of objects pictures in Rivermead Behavioral Memory Task. Contrary, we revealed significant impairment in delayed condition of remembering of the first and last name. There were no significant differences between the Sessions in Letter- and Semantic fluency tasks. Error bars indicate SEM.

In case of State-Trait Anxiety Inventory, we perceived significant improvement in state anxiety ($t(21) = 2.044, p = 0.054$) and trend of decreases in trait anxiety level ($t(21) = 1.897, p = 0.072$) (see in Figure 11). The mean duration of AHI index was correlated negatively with anxiety both in the diagnostic night (state anxiety: $r(19) = -0.573, p = 0.007$, trait anxiety: $r(19) = -0.573, p = 0.007$) and after two and half month of CPAP/BiPAP treatment (state anxiety: $r(20) = -0.576, p = 0.005$, trait anxiety: $r(20) = -0.576, p = 0.005$).

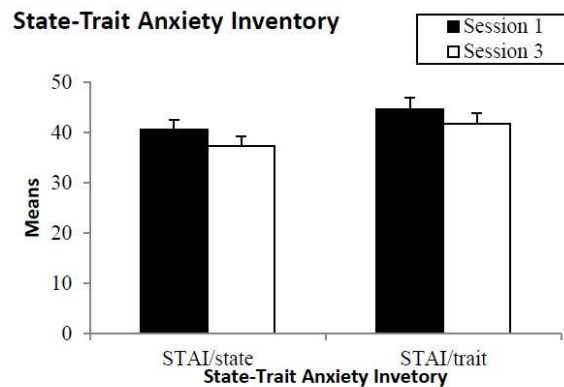


Figure 11. Results of state and trait anxiety before and after 2 and half month treatment: The OSA group showed significant improvement in state anxiety and trend of improvement in trait anxiety level. Error bars indicate SEM.

Correlation between sleep parameters and cognitive functions

We found significant moderate positive correlation between Letter Fluency Task and slow wave sleep ($r(13) = 0.535, p = 0.040$), the duration of NREM 4 sleep ($r(13) = 0.672, p = 0.006$) and the amount of delta waves in NREM 4 sleep ($r(13) = 0.7, p = 0.004$). In addition, Semantic Fluency Task was moderately correlated with the duration with NREM 4 sleep ($r(13) = 0.525, p = 0.045$), sleep spindles in NREM 3 ($r(13) = 0.723, p = 0.001$) and sleep spindles in NREM 4 ($r(13) = 0.674, p = 0.006$). These results indicated that increased slow waves activity resulted better performance in fluency task related to frontal lobe.

We observed that sleep spindles in NREM 3 and NREM 4 was moderately correlated with verbal working memory performance measured by Digit Span Task (S3 spindles: $r(13) = 0.535, p = 0.040$, S4 spindles: ($r(13) = 0.587, p = 0.022$), complex working memory measured by Backward Digit Span Task (S3 spindles: ($r(13) = 0.605, p = 0.017$, S4 spindles: ($r(13) = 0.629, p = 0.012$) and Listening Span Task (S3 spindles: ($r(13) = 0.703, p = 0.003$, S4 spindles: ($r(13) = 0.746, p = 0.001$).

Correlation between respiratory events, sleepiness and cognitive functions

We revealed moderate negative correlation between Letter Fluency Task and Respiratory Disturbance Index (RDI) ($r(12) = -0.694, p = 0.004$) and number of apnetic and hyponetic events (AHI events) ($r(21) = -0.494, p = 0.017$). Semantic Fluency Task also demonstrated high, negative correlation with RDI ($r(13) = -0.723, p = 0.002$) and AHI events ($r(21) = -0.453, p = 0.030$). Furthermore, the immediate ($r(13) = -0.556, p = 0.031$) and

delayed story recall ($r(13) = -0.595, p = 0.019$) in RBMT showed moderate negative correlation with RDI. Moreover, sleepiness measured by Epworth Sleepiness Scale showed moderate negative correlation with immediate story recall performance ($r(18) = -0.540, p = 0.014$) and executive functions measured by letter fluency task ($r(18) = -0.465, p = 0.039$).

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 learning phase, our results showed that children with SDB exhibited generally weaker declarative memory performance while the non-declarative performance 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 (Blunden et al., 2000; Gottlieb et al., 2004; Kaemingk et al., 2003; Kennedy 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 (Barlett et al., 2004; Halbower & Mahone, 2006; Halbower et al., 2006; Macey et al., 2002; Owens, 2009). 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-Gozalet 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; Hamasaki Uema et al., 2007). Moreover, these findings are similar to those of previous studies, which found no sleep-related improvement in non-declarative memory processes in healthy children (Backhaus et al., 2008; Prehn-Kristensen et al., 2009; Wilhelm et al., 2008). 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) (Genzel et al., 2009; Van Der Werf et al., 2011; Wilson et al., 2012). 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 the adult with OSA. For example, Kloepfer et al. (2009) found reduced overnight improvement on average RT performance in OSA patients using a very different task compared to ours (motor adaptation vs. sequence learning, respectively). 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 (Archbold et al., 2009; Cosentino et al., 2008; Naegele et al., 2006). The cause of this low working memory performance can be linked to the dysfunction of the frontal lobe (Cosentino et al., 2008). For instance, Thomas et al. (2005) found an absence of dorsolateral prefrontal activation during working memory task in patients with OSA.

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 (Archbold et al., 2009; Wilde et al., 2007). 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, Rouleau et al. (2002) found preserved learning measured by a sensorimotor adaptation task in OSA patients, although a subgroup of them demonstrated deficits in initial learning performance. This subgroup also had difficulties on other neuropsychological tests (e. g. executive functions). Naegele et al. (1995) using the same task also found significant but weaker learning in OSA than in the control group. The authors suggest that patients with OSA have difficulties creating new sensorimotor coordination. Moreover, our results are consistent with studies claiming no relationship between working memory and sequence-learning (Kaufman et al., 2010; McGeorge et al., 1997; Unsworth & Engle, 2005).

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. Kloepfer et al. (2009) found similar results: in the encoding, prior to sleep OSA patients showed similar non-declarative sensorimotor adaptation as the healthy control participants, but they revealed reduced overnight improvement on average RT performance. 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 the case of the offline changes of sequence-specific learning, we found similar performance between the OSA and control groups. This result is in line with previous studies that failed to find sleep-related changes in the consolidation of sequence-specific learning in healthy participants (Nemeth et al., 2010; Song et al., 2007). It suggests that sleep might have less influence on this specific

aspect of non-declarative learning. This conclusion is also supported by two recent reports. Song & Cohen (2014) propose that practice and sleep form different aspects of skill. Their results suggest transition learning (as in the ASRT) be an implicit component of skills that lacks sleep-dependence. In the other recent consolidation study, Meier and Cock (2014) found neither deterioration nor further improvement in sequence-specific learning over the offline period, however, they found offline improvement in general skill 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 (Heinzer et al., 2001; Verma et al., 2001; Morisson 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 (Bedard et al.,

1993; Borak et al., 1996). The possible explanation might be that these studies examined mild OSA patients after 3-month treatment. In our study, we measured moderate to severe OSA patients after 2 and half month therapy. In contrast to our results, Barnes et al. (2002) and Engleman et al. (1997) observed improvement in executive functions while we did not. The differences between the results might be explained by the type of the task (fluency task vs. neuropsychological assessment battery). Another possible explanation might be that previous studies examined mild OSA patients.

In the case of anxiety, our results are in line with previous studies which observed improvement in anxiety level after 1 month (Jokic et al., 1998) and 3 month PAP treatment (Engelman, Cheshire, Deary & Douglas, 1993). In contrast, Borak et al. (1996) and Munoz et al. (2000) found no improvement in anxiety neither 3 nor 9 months of PAP 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; Bedard et al., 1993; Redline & Strohl, 1998) or hypoxic events (Heinzer et al., 2001; Parrino et al., 2005; Thomas et al., 2005; Verma et al., 2001) or both (Engleman & Joffe, 1999; Ferini-Stambi et al., 2003; Jones & Harrison, 2001; Morisson et al., 2001) cause the cognitive decrement in obstructive sleep apnea. In our study, we found that both sleep disruption and intermittent hypoxia can lead to cognitive deficits. We revealed that executive function 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.

General conclusion

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 the 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.

Our findings underscore the importance of examining the effect of sleep disturbances on cognitive functions not only in children but also in adults. These studies can give us a deeper insight into the effect of sleep on the developing brain and memory functions and how the relationship between sleep and memory changes from childhood to adulthood. Our 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 non-declarative memory processes.

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Appendix

- 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.
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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, & Junghans, 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-Gozal, de Jong, Spruyt, Chamuleau, & Gozal, 2010) and deterioration of executive functions (Beebe & Gozal, 2002). For example, the former study by Kheirandish-Gozal 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

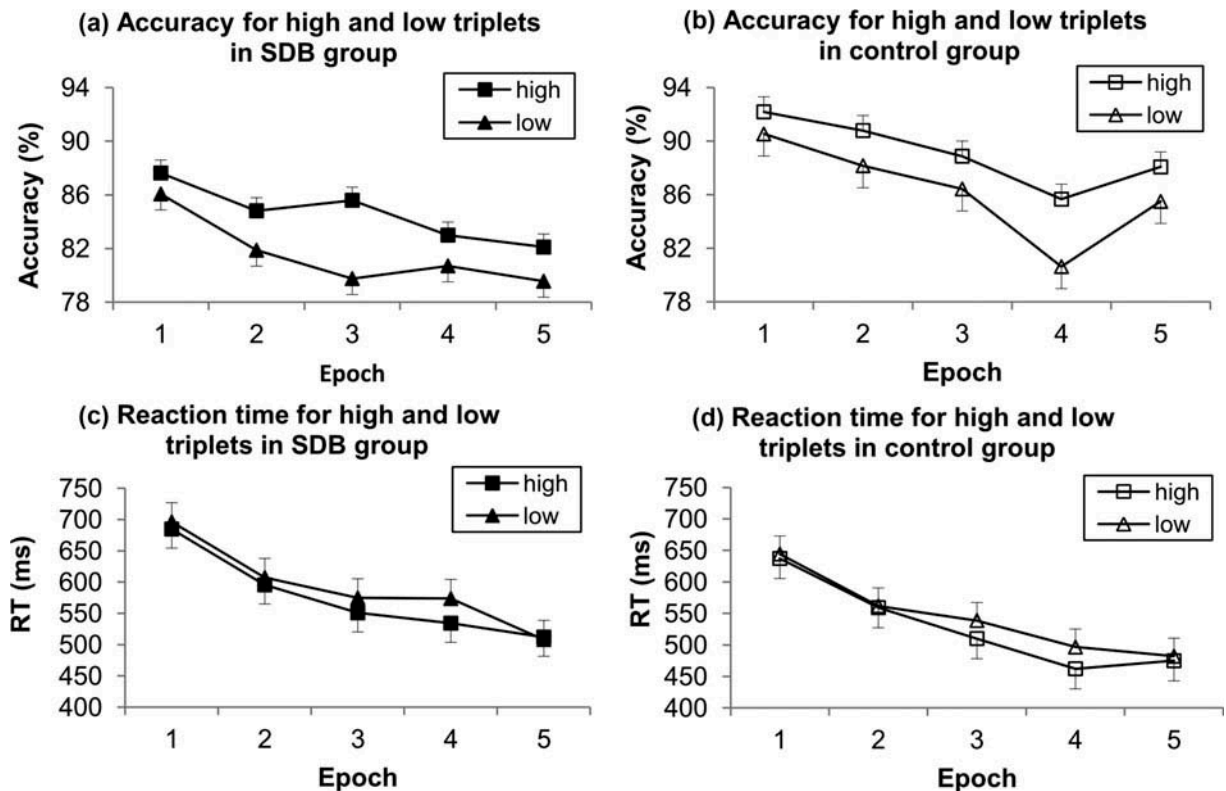


Figure 1. Results of accuracy for high and low triplets in (a) sleep-disordered breathing (SDB) and (b) control groups: Both groups showed significant sequence-specific learning, such that accuracy was greater on high- than on low-frequency triplets. There was a trend in general skill learning for accuracy 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).

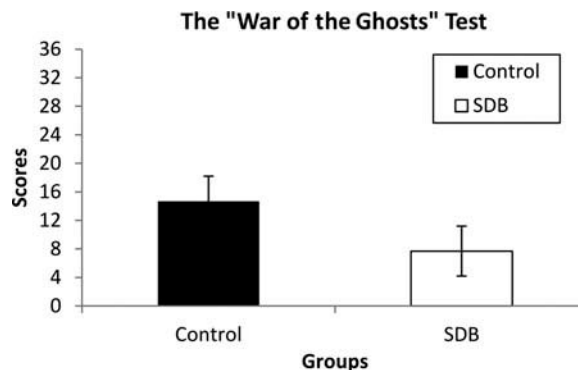


Figure 2. Declarative memory performance in sleep-disordered breathing (SDB) and control groups: The declarative memory performance of the SDB group was significantly lower than that of the control group. The dependent variable was the number of correctly recalled sentences. Error bars indicate standard 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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Declarative and Non-declarative Memory Consolidation in Children with Sleep Disorder

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Healthy sleep is essential in children's cognitive, behavioral, and emotional development. However, remarkably little is known about the influence of sleep disorders on different memory processes in childhood. Such data could give us a deeper insight into the effect of sleep on the developing brain and memory functions and how the relationship between sleep and memory changes from childhood to adulthood. In the present study we examined the effect of sleep disorder on declarative and non-declarative memory consolidation by testing children with sleep-disordered breathing (SDB) which is characterized by disrupted sleep structure. We used a story recall task to measure declarative memory and Alternating Serial Reaction time (ASRT) task to assess non-declarative memory. This task enables us to measure two aspects of non-declarative memory, namely general motor skill learning and sequence-specific learning. There were two sessions: a learning phase and a testing phase, separated by a 12 h offline period with sleep. Our data showed that children with SDB exhibited a generally lower declarative memory performance both in the learning and testing phase; however, both the SDB and control groups exhibited retention of the previously recalled items after the offline period. Here we showed intact non-declarative consolidation in SDB group in both sequence-specific and general motor skill. These findings suggest that sleep disorders in childhood have a differential effect on different memory processes (online vs. offline) and give us insight into how sleep disturbances affects developing brain.

Keywords: sleep deprivation, memory consolidation, declarative memory, skill learning, sequence learning, sleep-disordered breathing (SDB), implicit learning

INTRODUCTION

Healthy sleep is critical for children's cognitive, behavioral, and emotional development. Unfortunately, sleep disturbances are common in childhood, including both primary (e.g., insomnia and sleep apnea) and secondary sleep disorders (other illnesses e.g., depression or bad/altered sleep hygiene results the sleep disorders; Anuntaseree et al., 2001; Rosen et al., 2003; Bixler et al., 2009). The prevalence of sleep disorders in childhood estimates vary from 0.7 to 13% (Brunetti et al., 2001; Bixler et al., 2009). Therefore clinical research and practice need to focus more on sleep disturbances in children. The current study focuses on the effect of childhood sleep-disordered breathing (SDB) on declarative and non-declarative memory consolidation.

Memory consolidation can be defined as a set of processes whereby the newly acquired and initially labile memory traces become more stable with the passage of time (Stickgold and Walker, 2007; Spencer, 2013; Urbain et al., 2013). Growing body of evidence indicates that sleep plays a crucial role in these consolidation mechanisms and leads to memory representation being more resistant to interference and forgetting (Dorfberger et al., 2007; Diekelmann et al., 2009; Rudoy et al., 2009; Diekelmann and Born, 2010; Diekelmann, 2014; Mednick et al., 2011; Born and Wilhelm, 2012; Schönauer et al., 2014, 2015).

The effect of sleep on declarative (e.g., remembering events or facts) and non-declarative/procedural memory (e.g., learning languages, learning to musical instruments and movement-based sports) domains is well explored in healthy adults (Fischer et al., 2002; Walker et al., 2002; Gais and Born, 2004; Gais et al., 2006; Song et al., 2007; Rickard et al., 2008; Nemeth et al., 2010), but only a few studies focused on children. These studies with typically developing children found that post-training sleep facilitates the consolidation of declarative memory processes (Gais et al., 2006; Backhaus et al., 2008; Wilhelm et al., 2008; Prehn-Kristensen et al., 2009) but the effect of sleep on non-declarative memory consolidation is still controversial. Some studies failed to find a facilitating effect of sleep on non-declarative memory consolidation (Wilhelm et al., 2008; Prehn-Kristensen et al., 2009), however some recent studies revealed that sleep impacts on non-declarative/procedural memory in children (Fischer et al., 2007; Wilhelm et al., 2012, 2013; Urbain et al., 2013). In contrast to these results, Fischer et al. (2007) demonstrated offline decrement after sleep in non-declarative memory in children compared to adults who showed offline improvement after sleep. In a recent study Borragán et al. (2015) clarified the picture by showing that sleep has a beneficial effect on the consolidation of motor skills but it has no influence on sequential skills. These results indicate that sleep-dependent non-declarative memory consolidation can depend on age (Fischer et al., 2007; Wilhelm et al., 2008) and the nature of the task (Wilhelm et al., 2008, 2012; Borragán et al., 2015). Less is known about how permanent sleep-disorder influences sleep-dependent consolidation of declarative and non-declarative memories in children.

In our study we examined children with SDB which is an ideal population to investigate the effects of sleep disorder on the consolidation of different memory systems. SDB is a spectrum disorder characterized by prolonged and intermittent partial (such as snoring) or complete upper airway obstruction (such as Obstructive sleep apnea, OSA) that disturbs normal ventilation and sleep pattern during sleep. Especially slow wave sleep and REM sleep are affected in SDB (Coleman, 2003; Li and Lee, 2009; Sinha and Guilleminault, 2010). OSA is the worst grade on this spectrum characterized by repetitive episodes of complete or partial upper airway obstruction during sleep resulting hypoxia and fragmented sleep (Banno and Kryger, 2007). The main cases of SDB in children is with adenotonsillar hypertrophy, but it also occurs with obesity, upper airway narrowing due to craniofacial or neuromuscular abnormalities or muscular coordination

(Arens et al., 2001; Guimaraes et al., 2008; Katz and D'Ambrosio, 2008).

The neurocognitive consequences of SDB in children have not yet been fully evaluated. There is emerging evidence that cognitive deficits are most consistently apparent on tasks involving sustained attention and executive functions (Beebe and Gozal, 2002; Archbold et al., 2004; O'Brien et al., 2004b; Beebe, 2006). In addition, SDB is associated with deterioration of memory; for example, Gottlieb et al. (2004) revealed that children with SDB had significantly poorer performance on verbal (Narrative Memory) and visual memory tasks (Memory for Faces) compared to healthy participants. Kheirandish-Gozal et al. (2010) investigated the learning before sleep (acquisition) and delayed free recall performance after an overnight sleep (retention) in children with OSA compared with children without sleep disorder. They used pictorial-based memory task where the subjects required to learn and remember animal pictures. They found that both immediate (before sleep) and delayed recall performances (after sleep) were worse among OSA children compared to the control subjects. The authors suggested that this reduced performance may be caused by impaired ability to use adequate learning strategies which either leads to difficulties to learn new information or children with OSA suffer from impaired encoding or altered retrieval. In our recent study (Csábi et al., 2013), we investigated declarative and non-declarative memory performance in one learning session (without consolidation) and showed weaker declarative but intact non-declarative memory performance in children with SDB compared to the controls. These results suggest that the more attention-demanding declarative learning are more vulnerable to permanent sleep disorder than less attention demanding non-declarative learning.

The mechanisms causing these neuropsychological deficits have not been fully delineated. Previous studies suggest that the developing central nervous system in children may be relatively more vulnerable to the fragmented sleep and hypoxia, particularly the hippocampus and frontal lobe structures (Macey et al., 2002; Morrell et al., 2003; Bartlett et al., 2004; Halbower et al., 2006; Owens, 2009). Children with SDB can exhibit daytime behavioral regulation problems (such as inattention, hyperactivity, aggressiveness, social withdrawal) which might also imply frontal lobe dysfunction (Chervin and Archbold, 2001; Beebe and Gozal, 2002; Archbold et al., 2004; Archbold, 2006).

Previous studies examined memory encoding and consolidation before and after sleep in patients with sleep apnea in adults, and showed that declarative and some aspects of non-declarative memory performance is affected in patients with OSA (Kloepfer et al., 2009; Djonlagic et al., 2012; Csabi et al., 2014). Similarly to Borragán et al. (2015) we found dissociation in the effect of sleep (and/or sleep disorder) on offline changes of general motor skills and sequence-specific learning: adult OSA patients showed impaired consolidation of general motor but not on sequence-specific learning (Csabi et al., 2014). To our knowledge, the current study is the first to assess the effects of sleep disorder on declarative and non-declarative memory

functions before and after a nighttime sleep in children. Based on previous studies, we hypothesized that SDB in childhood has an adverse effect on the consolidation of declarative memory while it has less influence on non-declarative memory consolidation. Within the later one we expect differences in the consolidation of motor and sequence-specific aspects of the offline changes.

MATERIALS AND METHODS

Participants

Thirty two children participated in the experiment. Breathing events during sleep, Body Mass Index (BMI) and working memory (WM) measures of the SDB patients and healthy participants are listed in **Table 1**. All participants underwent an overnight polygraphy, which was performed with the Somnomedics Somnoscreen plus device (Randersacker, Germany) at the Sleep Disorders Laboratory of Heim Pál Children's Hospital, Budapest, Hungary. Patients who met the International Classification of Sleep Disorders criteria's (American Academy of Sleep Medicine, 2001) for SDB were included in the study. SDB was diagnosed by a board-certified sleep physician. The SDB group consisted of sixteen children with SDB (average age: 8.56 years [min: 6 to max: 11 years], SD : 2.31; 6 females/10 males) six of them with OSA and ten of them with primary snoring. The Apnea/Hypopnea (AHI) index of the OSA patients ($M = 17.32$, $SD = 30.54$, range 2–79) was significantly higher (all p 's < 0.01) than that of the snoring patients ($M = 0.11$, $SD = 0.19$, range 0–1) as well as the controls ($M = 0.11$, $SD = 0.20$, range 0–1). Similarly, the snore index of the snoring patients ($M = 55.10$, $SD = 54.95$, range 6–155) was significantly higher (all p 's < 0.03) than

that of the OSA patients ($M = 16.67$, $SD = 28.52$, range 0–73) as well as the controls ($M = 0.13$, $SD = 0.34$, range 0–1). According to the literature, the neurobehavioral deficits is associated with snoring in children are similar to those found in children with OSA (Gozal and O'Brien, 2004; O'Brien et al., 2004a). Therefore we compared the performance of the SDB group to that of controls and did not intend to examine the OSA and snoring subgroups separately. All SDB patients were untreated prior to and during the experimental night in the sleep laboratory.

The control group consisted of sixteen healthy participants (average age: 8.75 years, SD : 1.44 [min: 6 to max: 15 years]; 8 females/8 males). The control and the patient groups were matched on age ($t_{(30)} = 0.28$, $p = 0.78$) and gender ($\chi^2_{(1)} = 0.51$, $p = 0.48$) and parental education (mother education: $t_{(12.54)} < 0.001$, $p > 0.99$; father education $t_{(23)} = 0.61$, $p = 0.55$). 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 any financial compensation for their participation. Ethics approval was obtained by the Ethics Committee at Heim Pal Children's Hospital, Budapest.

TASKS

Tasks

Story Recall—"The War of the Ghosts" Test

Declarative memory performance was measured by "The War of the Ghosts" test (Bartlett, 1932; Bergman and Roediger, 1999). This is a story recall test, which is widely used to measure declarative memory for episodes (Bartlett, 1932; Bergman and Roediger, 1999; Andreano and Cahill, 2006, 2008; Schwabe and Wolf, 2009; Hardt et al., 2010). In this test children are asked to listen and repeat the story after various intervals (immediately or after a determinate interval). 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 of the sentences; Bartlett, 1932; Gauld and Stephenson, 1967; Csábi et al., 2013).

Alternating Serial Reaction time (ASRT) Task

We used a modified version of the original ASRT task in order to assess non-declarative/procedural 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 and Howard, 1997). In our version, a dog's head appeared in one of the four empty circles on the screen and participants had to press the corresponding button (Nemeth et al., 2010). The computer was equipped with a special keyboard with four marked keys (Y, C, B and M on a QWERTZ keyboard; thus, compared to the English keyboard layout, the location of the buttons Z and Y were switched), each corresponding to one of the horizontally aligned circles. Before beginning the task, detailed instructions were read to the

TABLE 1 | Means (standard deviations) of participants' data are presented in the table.

	Control ($n = 16$)	SDB ($n = 16$)	t (df)	p -value
Snore index events/hour	0.13 (0.34)	40.69 (49.52)	-3.28 (15.001)	0.005**
AHI event/hour	0.11 (0.20)	6.56 (19.62)	-1.31 (15.003)	0.21
Max. desaturation (%)	92.31 (4.13)	90.56 (7.75)	0.80 (30)	0.43
Desaturation index (%)	0.56 (0.89)	11.25 (26.76)	-1.60 (15.003)	0.13
BMI kg/m ²	15.19 (1.22)	19.25 (5.17)	-3.06 (16.67)	0.01*
Counting span	2.88 (0.72)	2.48 (0.55)	1.74 (30)	0.09+
Listening span	2.40 (0.75)	2.16 (1.09)	0.72 (30)	0.48
Digit span	4.81 (0.65)	4.50 (0.89)	1.13 (30)	0.27

Snore Index: snoring events per hour; AHI: Apnea-Hypopnea Index: apnetic and hypopnetic events per hour of sleep; Max. desaturation: ratio of oxihemoglobin to the total concentration of hemoglobin present in the blood; Desaturation Index: number of time/hour of sleep that the blood's oxygen level drops by 3% or more for baseline; BMI: body mass index kg/m². Listening Span Task: a working memory (WM) task in which the participants are required to listen to increasingly longer sequences of sentences and to recall the final word of all the sentences in each sequence in serial order (Daneman and Blennerhassett, 1984). Counting Span Task: a WM task in which participants are required to count a growing number of colored dots on the computer screen and remember the number of the dots of each sequence (Case et al., 1982; * $p < 0.05$, ** $p < 0.01$, + $p < 0.10$).

participants. We emphasized that the aim was to try to respond as quickly and as correctly as possible. Session 1 (Learning Phase) consisted of 25 blocks, with 85 key presses in each block—the first five stimuli were random for practice purposes, then an 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) repeated ten times. This sequence structure is often described as non-adjacent second-order dependency (Remillard, 2008). Similarly to earlier studies (Nemeth et al., 2010), stimuli were presented 120 ms after the previous response (response-to-stimulus interval, RSI). Each block required about 1.5 min and the entire session took approximately 30–40 min. Between blocks, participants received feedback about their overall RT and accuracy on the screen and then rested 10–20 s before starting a new block. Session 2 (Testing Phase) consisted of 5 blocks; the number of key presses and the RSI were the same as in Session 1 and this Testing Phase took approximately 5–10 min to complete.

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 task 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 could be derived from the sequence or could also be a random element. In contrast, 1_2 or 4_1 would occur less frequently because in this case the third element could only be random. Following previous studies (Howard and Howard, 1997; Song et al., 2007; Nemeth et al., 2010), we refer to the former as high-frequency triplets and the latter as low-frequency triplets. Out 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 compared to the low-frequency triplets.

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 and Howard, 1997; Howard et al., 2004; Song et al., 2007; Nemeth et al., 2010; Janacsek et al., 2012). In addition, general motor skill learning is revealed in the ASRT task by the overall speed-up due to practice, irrespective of the triplet types. Thus, using the ASRT task enables to measure both sequence-specific and general motor skill learning.

Procedure

There were two sessions in the experiment. The declarative and non-declarative performance was assessed at 7–9 PM prior to sleep (Learning Phase/Session 1) and 7–9 AM after sleep (Testing Phase/Session 2), thus the average interval between the Learning and Testing Phase was 12 h. The order of the administration of declarative and non-declarative tasks was counterbalanced in

order to minimize the interference between declarative and non-declarative tasks (see Brown and Robertson, 2007).

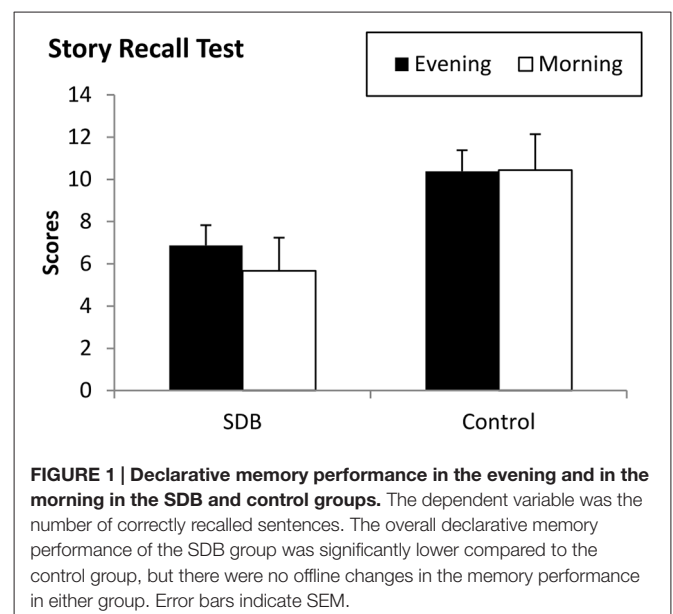
Statistical Analysis

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, etc. We calculated mean accuracy and median RT 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 and Howard, 1997; Song et al., 2007; Nemeth et al., 2010), 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 and Howard, 1997; Howard et al., 2004). By eliminating them we attempted to ensure that any high- vs. low-frequency differences are due to learning and not to pre-existing tendencies.

RESULTS

Story Recall Test

We conducted a mixed design ANOVA with SESSION (1–2) as a within-subject factor and GROUP (SDB vs. control) as a between-subject factor to assess offline changes in declarative memory performance. The main effect of GROUP was significant ($F_{(1,29)} = 6.155$, $\eta_p^2 = 0.175$, $p = 0.019$), indicating weaker story recall performance in the SDB compared to the controls (6.267 vs. 10.406, respectively). This weaker performance of the SDB group compared to the control group was evident both in Session 1 (6.87 vs. 10.38; $p = 0.03$) and in Session 2 (5.67 vs. 10.44; $p = 0.01$; Figure 1).



The main effect of SESSION failed to reach significance ($F_{(1,29)} = 2.05$, $\eta_p^2 = 0.06$, $p = 0.16$), suggesting no change in the performance during the offline period. Similarly, the SESSION \times GROUP interaction was not significant either ($F_{(1,29)} = 2.53$, $\eta_p^2 = 0.08$, $p = 0.12$), suggesting no differences in offline changes between the SDB and control groups.

Accuracy Analysis in the ASRT Task

Online Learning During Session 1 (Learning Phase)

A mixed design ANOVA was conducted on the 5 epochs of the data shown in **Figure 2** 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: $F_{(1,30)} = 61.26$, $\eta_p^2 = 0.67$, $p < 0.001$), 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: $F_{(1,30)} = 0.29$, $\eta_p^2 = 0.01$, $p = 0.59$).

The main effect of EPOCH did not reach significance ($F_{(4,120)} = 2.58$, $\eta_p^2 = 0.07$, $p = 0.06$), although accuracy decreased across epochs on a trend level. SDB and control groups performed at the same level (EPOCH \times GROUP interaction: $F_{(4,120)} = 1.29$, $\eta_p^2 = 0.04$, $p = 0.28$).

The TRIPLET \times EPOCH interaction was significant ($F_{(4,120)} = 3.37$, $\eta_p^2 = 0.10$, $p = 0.01$), but there were no significant differences between the groups (indicating by the TRIPLET \times EPOCH \times GROUP interaction $F_{(4,120)} = 0.41$, $\eta_p^2 = 0.01$, $p = 0.79$; respectively), demonstrating that the pattern of learning was similar in the groups. The main effect of GROUP did not reach significance ($F_{(1,30)} = 3.91$, $\eta_p^2 = 0.11$, $p = 0.06$), although the SDB group had lower accuracy on a trend level (SDB group: 88.6%, control group: 91.8%).

Offline Changes of Sequence-Specific and General Motor Skill Learning

To investigate the offline changes of sequence-specific and general motor skill learning we compared the accuracy from the last epoch of Session 1 (Epoch 5) and the epoch of Session 2 (Epoch 6) in both groups. These variables were submitted to a mixed design ANOVA with TRIPLET (2: high- vs. low-frequency) and EPOCH (2: last epoch of Session 1 and epoch of Session 2) as within-subject factors, and GROUP (SDB vs. control) as a between-subject factor. The data is shown in **Figure 2**.

There was significant sequence-specific learning (indicating by the main effect of TRIPLET; $F_{(1,30)} = 95.40$, $\eta_p^2 = 0.76$, $p < 0.001$), such that accuracy was greater on high- than on low-frequency triplets. It was similar in the SDB and control groups (indicated by the non-significant TRIPLET \times GROUP interaction: $F_{(1,30)} = 0.04$, $\eta_p^2 = 0.002$, $p = 0.82$).

There was a significant offline changes of general motor skills (indicating by the main effect of EPOCH; $F_{(1,30)} = 13.40$, $\eta_p^2 = 0.30$, $p = 0.01$), thus accuracy increased from evening to morning. SDB and control groups performed at the same

level (EPOCH \times GROUP interaction: $F_{(1,30)} = 3.26$, $\eta_p^2 = 0.09$, $p = 0.08$).

The TRIPLET \times EPOCH and TRIPLET \times EPOCH \times GROUP interactions were not significant ($F_{(1,30)} = 0.20$, $\eta_p^2 = 0.01$, $p = 0.65$; $F_{(1,30)} = 0.28$, $\eta_p^2 = 0.01$, $p = 0.59$; respectively), indicating that the pattern of sequence-specific learning was similar in the groups. The main effect of GROUP was not significant ($F_{(1,30)} = 1.31$, $\eta_p^2 = 0.04$, $p = 0.26$), reflecting that all groups responded with similar accuracy rates (SDB group: 88.8%, control group: 91.2%).

Reaction Time Analysis in the ASRT Task

Online Learning During Session 1 (Learning Phase)

To investigate learning during Session 1, a mixed design ANOVA was conducted on the first 5 epochs of the data shown in **Figure 3**, with TRIPLET (2: high- vs. low-frequency) and EPOCH (5: 1–5) as within-subject factors, and GROUP (SDB vs. control) as a between-subject factor.

Our data revealed significant sequence-specific learning (indicated by the significant main effect of TRIPLET: $F_{(1,30)} = 64.33$, $\eta_p^2 = 0.68$, $p < 0.001$), such that RTs were faster on high- than on low-frequency triplets. SDB and control groups showed no differences in sequence-specific learning (TRIPLET \times GROUP interaction: $F_{(1,30)} = 0.59$, $\eta_p^2 = 0.04$, $p = 0.44$).

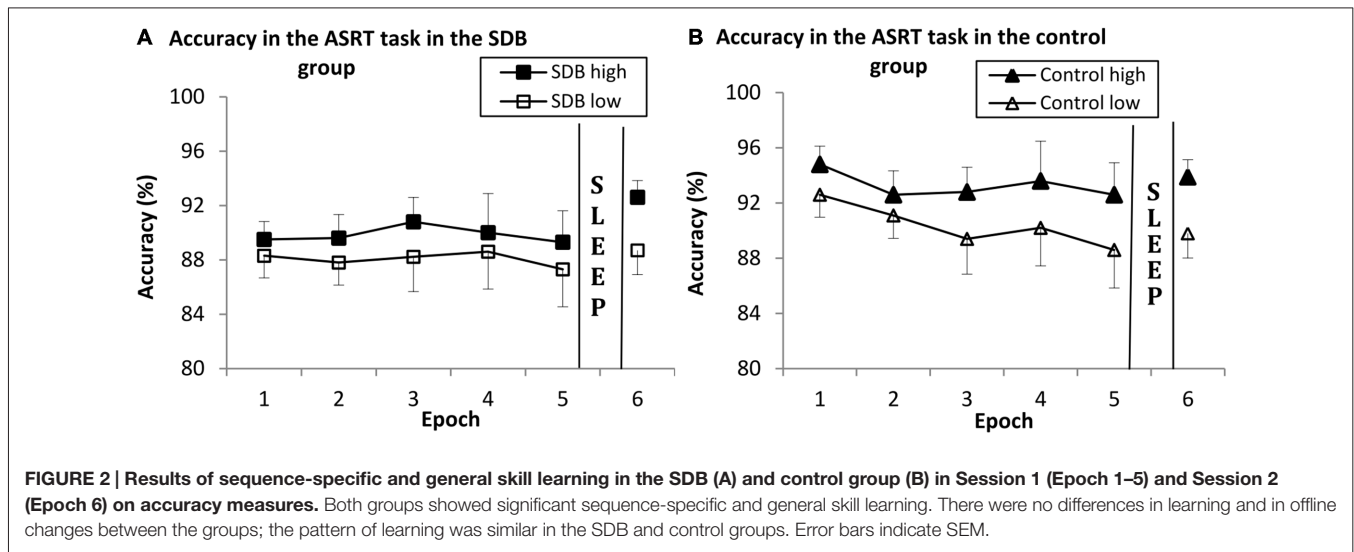
There was also significant general motor skill learning (shown by the significant main effect of EPOCH: $F_{(4,120)} = 54.80$, $\eta_p^2 = 0.64$, $p < 0.001$), such that RTs decreased across epochs. SDB and control groups performed at the same level (EPOCH \times GROUP interaction: $F_{(4,120)} = 0.95$, $\eta_p^2 = 0.03$, $p = 0.38$).

The TRIPLET \times EPOCH interaction was significant ($F_{(4,120)} = 5.26$, $\eta_p^2 = 0.14$, $p = 0.003$), suggesting that sequence-specific knowledge increased during practice. The TRIPLET \times EPOCH \times GROUP interaction was not significant ($F_{(4,120)} = 0.49$, $\eta_p^2 = 0.013$, $p = 0.67$), indicating that the pattern of learning was similar in the groups. In overall RT both group performed at the same level (main effect of GROUP: $F_{(1,30)} = 1.37$, $\eta_p^2 = 0.04$, $p = 0.25$).

Offline Changes of Sequence-Specific and General Motor Skill Learning

To investigate the offline changes of sequence-specific and general motor skill learning we compared the RTs from the last epoch of Session 1 (Epoch 5) and the epoch of Session 2 (Epoch 6) in both groups. These variables were submitted to a mixed design ANOVA with TRIPLET (2: high- vs. low-frequency) and EPOCH (2: last epoch of Session 1 and epoch of Session 2) as within-subject factors, and GROUP (SDB vs. control) as a between-subject factor. The data is shown on **Figure 3**.

There was significant sequence-specific learning (indicating by the main effect of TRIPLET; $F_{(1,30)} = 125.76$, $\eta_p^2 = 0.80$, $p < 0.001$), thus RTs were faster on high- than low-frequency triplets when analysing the two epochs together. The groups did not differ in overall sequence-specific learning (indicated by the



non-significant TRIPLET \times GROUP interaction: $F_{(1,30)} = 0.42$, $\eta_p^2 = 0.01$, $p = 0.51$).

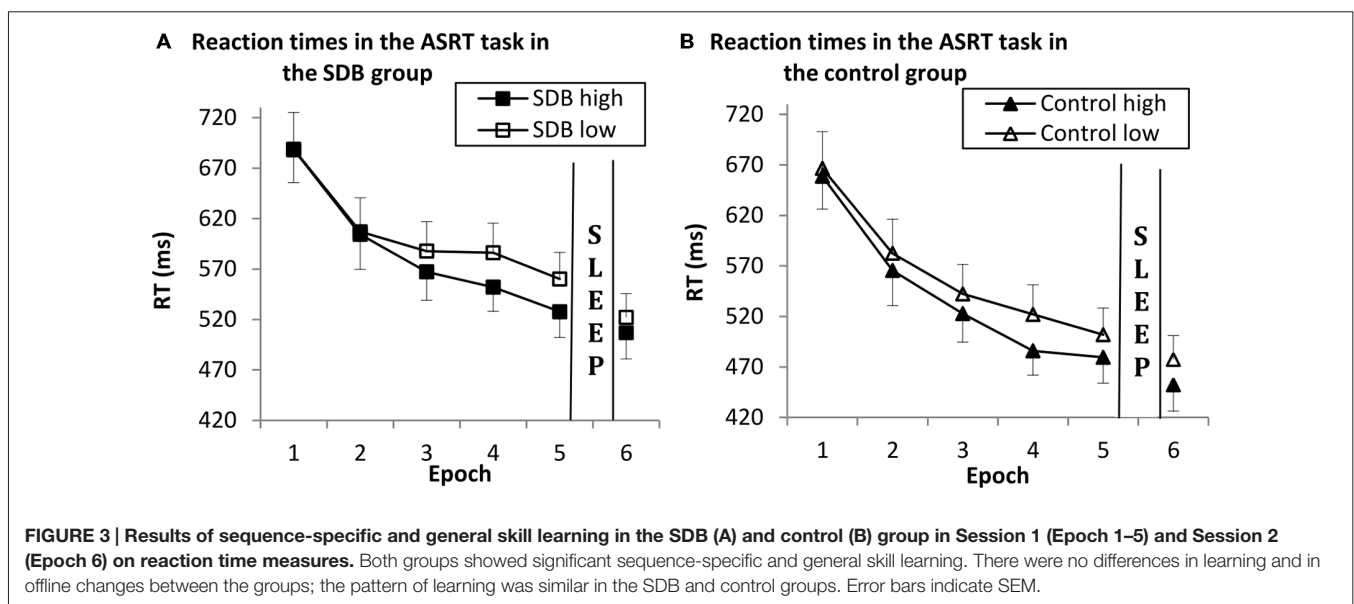
There was significant general motor skill learning during the offline period (demonstrated by the main effect of EPOCH: $F_{(1,30)} = 20.71$, $\eta_p^2 = 0.40$, $p < 0.001$), such that RTs were faster in the morning compared to the evening. The SDB and control groups showed similar level of offline general motor skill learning (EPOCH \times GROUP interaction: $F_{(1,30)} = 0.24$, $\eta_p^2 = 0.01$, $p = 0.62$).

The TRIPLET \times EPOCH and the TRIPLET \times EPOCH \times GROUP interactions were not significant ($F_{(1,30)} = 0.84$, $\eta_p^2 = 0.02$, $p = 0.36$; $F_{(1,30)} = 2.18$, $\eta_p^2 = 0.06$, $p = 0.15$, respectively), indicating that the SDB and the control group demonstrated no differences in the pattern of offline changes. There were no significant differences in the overall RTs between the SDB and

control groups (main effect of GROUP: $F_{(1,30)} = 2.54$, $\eta_p^2 = 0.07$, $p = 0.12$).

DISCUSSION

Our goal was to investigate the consolidation of declarative and non-declarative memory in children with SDB. We believe our study to be the first to investigate the offline changes of these two types of memory processes in children with sleep disorder. We found no group difference in the consolidation of declarative memory; the SDB group, however, showed generally weaker memory performance in both sessions. We used the ASRT task to measure non-declarative learning processes. This sequence learning task allowed us to differentiate between two components of learning: general motor skill learning and



sequence-specific learning. We found that these two types of non-declarative learning and consolidation are intact in children with SDB.

Our results on online declarative memory performance are in line with previous studies that found weaker declarative performance in the SDB group in general (Blunden et al., 2000; Kaemingk et al., 2003; Gottlieb et al., 2004; Kennedy et al., 2004; Csábi et al., 2013). Gottlieb et al. (2004) found lower performance on verbal and visual memory tasks in children with SDB compared to healthy controls. The mechanism causing these neuropsychological deficits has not been fully explored. Results from previous studies suggest that sleep fragmentation and intermittent hypoxia could have negative influence on the development of the central nervous system resulting structural changes in brain circuits, particularly in the hippocampus and frontal lobe (Macey et al., 2002; Bartlett et al., 2004; Halbower et al., 2006; Owens, 2009). For example Bartlett et al. (2004) found that in the left hippocampal area, N-acetyl-containing/creatine-containing compounds was significantly increased in adult OSA patients using proton magnetic resonance spectroscopic imaging. In childhood OSA Halbower et al. (2006) showed also significant differences in the mean metabolite ratio N-acetyl in the left hippocampus and right frontal cortex compared to controls leading the conclusion that childhood OSA is associated with neuronal injury in the hippocampus and frontal cortex. It is important to note that we assessed only the breathing indices during sleep. Further investigations using polysomnography need to clarify the relationship between declarative memory functions and sleep stages or sleep deprivation in children with SDB.

In the case of the overnight consolidation of declarative memory, we failed to find differences between the SDB and control group. Although there was a general group difference in the overall performance, both groups showed intact consolidation. This result contradicts with the finding of Kheirandish-Gozal et al. (2010) who demonstrated decreased consolidation of declarative memory in children with OSA. The difference between the two studies might be explained by the type of materials to be remembered (verbal vs. nonverbal) and other task characteristics (e.g., number of repetitions). Another possible explanation might be that the SDB group in our study demonstrated a floor effect with no room to forget in the offline period. For example, compared to the healthy controls, sleep disturbances in the SDB group can lead to a greater fatigue effect, which can be more pronounced by the evening where the first session took place, and could lead to weaker memory performance in the SDB group. This explanation can be tested by controlling for circadian effects and comparing AM-PM vs. PM-AM designs. Future studies need to unravel how task characteristics and/or circadian factors affect sleep-related declarative memory consolidation in children.

In the case of non-declarative learning, we found similar performance between the SDB and control group in general motor skill and sequence-specific learning in the Learning Phase, both in accuracy and in RT. Our results are in line with our previous study in which the SDB group showed impaired declarative memory performance while the non-declarative

learning remained intact compared to the healthy controls (Csábi et al., 2013). Nemeth et al. (2012) using the ASRT task also found intact non-declarative sequence learning in elderly adults with OSA. These results indicate that the relationship between online non-declarative memory formation and sleep is similar in children and adults with SDB. The performance difference between declarative and non-declarative tasks in session one can be explained by that the disrupted sleep pattern influences the more attention-demanding and cortical structure-guided explicit processes (story recall), while the less attention-demanding implicit processes (ASRT task) mediated by subcortical structures are preserved (Csábi et al., 2013).

In the overnight consolidation of non-declarative memory we found no differences in the offline changes of either general motor skill or sequence-specific learning between the two groups. We found offline improvement on general motor skill, while the sequence-specific learning remained on the same level and did not improve. To our knowledge, consolidation of non-declarative memory has not been tested in children with SDB yet. These results are in line with studies investigating the effect of sleep deprivation on non-declarative sequence learning in adults without sleep disorder (Genzel et al., 2009; Van Der Werf et al., 2011). There are a few studies investigating non-declarative memory consolidation in adults with OSA. For example, Kloepfer et al. (2009) found reduced overnight improvement on average RT performance in OSA patients using a very different task compared to ours (motor adaptation vs. sequence learning, respectively). 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. In our previous study with adult OSA patients, we revealed differences in the offline changes of general motor skill learning between the OSA and control group. The control group showed offline improvement on general motor skill learning from evening to morning, while the OSA group did not. In contrast, we did not find differences between the groups in offline changes in sequence-specific learning (Csabi et al., 2014). These results partly differ from our current findings and highlight the importance of developmental factors in the consolidation of non-declarative memory: sleep disordered breathing might affect the underlying neural network differently in childhood compared to adulthood.

It worth mentioning that our study have two important potential limitations. Firstly, the declarative and non-declarative tasks could be interfere to each other. For example Brown and Robertson (2007) found that declarative tasks can actually boost non-declarative learning. It is possible that our manipulation namely counterbalancing these two types of task is not enough to eliminate the interference. Secondly, it is possible that the actual story recall task is not sensitive enough to demonstrate sleep effect. Further studies need to clarify these issues by examining the declarative and non-declarative tasks separately in different experiments and using other type of declarative tasks as well.

In conclusion, our study found dissociation between the declarative and non-declarative processes in children with SDB. Similarly with Csábi et al. (2013) we found weaker declarative memory than non-declarative performance in the first Session (Learning Phase). Regarding the consolidation, we found intact consolidation in the case of declarative memory as well as sequence-specific and general motor skill aspects of non-declarative memory in SDB. These findings imply that actual and/or long-term disturbance of sleep has a differential effect on different memory processes (online vs. offline). Our findings underscore the importance of examining the effect of sleep disturbances on motor and cognitive functions in childhood. These studies can give us a deeper insight into the effect of sleep on the developing brain and memory functions and how the relationship between sleep and memory changes from childhood

to adulthood. Since persistent sleep problems in childhood can lead not only to impaired cognitive functioning—consequently lower general intelligence and school performance—but also anxiety and depression disorders in adulthood (Gregory et al., 2005), these results can help us develop more sophisticated diagnostic tools, neuropsychological profile and more effective rehabilitation programs.

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Intact implicit probabilistic sequence learning in obstructive sleep apnea

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SUMMARY

Obstructive sleep apnea (OSA) belongs to the sleep-related breathing disorders and is associated with cognitive impairments in learning and memory functions. The impairments in attention-demanding cognitive functions such as working memory and executive functions are well established in OSA; however, it remains unknown if less attention-demanding implicit sequence learning is affected. In the present study, we examined implicit sequence learning in OSA to probe the functional integrity of this fundamental learning mechanism. We used listening span to measure complex working memory capacity and the alternating serial reaction time (ASRT) task, which enables us to measure general skill learning and sequence-specific learning separately. Twenty OSA patients and 20 healthy controls participated in this study. Our data show dissociation between working memory and implicit sequence learning in OSA. Surprisingly, OSA patients showed preserved general skill and sequence-specific learning in spite of the possible hypoxia and sleep restriction. In contrast, working memory performance measured by listening span task was impaired in the OSA group. This finding suggests selective susceptibility of more attention-demanding cognitive functions in this patient population, while implicit learning remains intact. Our findings draw attention the fact that disordered sleep may have less impact on the integrity of structures connected to implicit sequence learning.

INTRODUCTION

Implicit sequence learning occurs when information is acquired from an environment of complex stimuli without conscious access to either what was learned or to the fact that learning occurred (Howard *et al.*, 2004). Implicit sequence learning underlies not only motor but cognitive and social skills as well (Lieberman, 2000; Nemeth *et al.*, 2011; Romano Bergstrom *et al.*, 2011); it is therefore an important aspect of life from infancy to old age. Implicit sequence learning is essential for learning languages, for learning to operate computer applications and musical instruments (Howard *et al.*, 2004). Most models and empirical studies of sequence learning highlight the role of the basal ganglia (Daselaar *et al.*, 2003; Hikosaka *et al.*, 1999; Kincses *et al.*, 2008; Rieckmann *et al.*, 2010; Sefcsik *et al.*, 2009), while the

role of the hippocampus, frontal and parietal areas remains inconclusive (Albouy *et al.*, 2008; Gheysen *et al.*, 2010; Pascual-Leone *et al.*, 1996; Schendan *et al.*, 2003). The role of sleep on the ability to implicitly learn novel material has not been characterized comprehensively so far. Obstructive sleep apnea (OSA) is an ideal field to investigate the interaction between sleep and implicit learning because OSA is characterized by repeated episodes of upper airway obstruction during sleep, resulting in hypoxia which leads to repetitive arousals from sleep, thus disturbing the normal sleep pattern (Banno and Kryger, 2007). In OSA only a few studies have examined cognitive functions related to sub-cortical structures. Therefore, in the present study, we examined implicit sequence learning in OSA to probe the functional integrity of this type of fundamental learning mechanism.

Some studies have examined implicit learning in patients with OSA (Naegele *et al.*, 2006); however, only a few studies have used sequence learning [e.g. finger-tapping, serial reaction time (RT) task] to measure implicit motor learning. Lojander *et al.* (1999) have demonstrated poor performance on the finger-tapping task in apnea patients. By contrast, other studies (Archbold *et al.*, 2009; Wilde *et al.*, 2007) found intact performance on this task, but impaired word recall and working memory performance.

In our study we used the alternating serial reaction time (ASRT) task to investigate implicit sequence learning in OSA. This task enables us to separate general skill learning and sequence-specific learning. In the ASRT task, recurring elements alternated with random elements in an eight-element sequence, so that the location of every second stimulus in the stream is determined randomly (e.g. 1R2R3R4R, where the numbers represent the recurring elements, and R represents random stimuli). This sequence structure has been termed 'probabilistic second-order dependency' (Remillard, 2008). The repeating sequence in the ASRT task is more complex and better hidden than in the classical SRT tasks or finger-tapping tasks, so that the task relies more on implicit mechanisms of learning (Song *et al.*, 2007). To our knowledge, this type of complex implicit sequence learning has not yet been studied in OSA. We also examined the working memory performance of OSA patients to investigate whether the less attention-demanding implicit sequence learning and the more attention-demanding working memory show differences. Prior reports in healthy participants found no relationship between the two systems (Feldman *et al.*, 1995; Kaufman *et al.*, 2010; McGeorge *et al.*, 1997; Unsworth and Engle, 2005; for opposite findings see Bo *et al.*, 2011; Frensch and Miner, 1994). The frontal lobe-related attentional processes are influenced mainly by disrupted sleep architecture (Hobson, 2009; Muzur *et al.*, 2002). Therefore, we can predict that the working memory is more affected compared to less attention-demanding implicit sequence learning in OSA.

MATERIALS AND METHODS

Participants

Twenty untreated participants were included in the OSA group [average age: 52.70, standard deviation (SD) 9.60; average education: 11.95, SD: 2.62, three female/17 male]. OSA was diagnosed by a board-certified sleep physician based on a full night of clinical polysomnography. The mean apnea-hypopnea index (AHI) was 50.76 event per hour SD: 22.20 (range: 21.10–117.30). The pathological level of AHI was defined as 15 or more per hour (Banno and Kryger, 2007). The mean of respiratory disturbance index (RDI) in total sleep time was 60.97 event per hour SD: 16.76 (range: 33.10–86.80). RDI was calculated as the number of respiratory events [respiratory effort-related arousal (RERA) + apneas + hypopneas] per hour of sleep. Pathological level

of RDI defined as 10 or more per hour (Peker *et al.*, 2000). The mean of the daytime sleepiness measured by the Epworth Sleepiness Scale was 10.00, SD: 4.44 (range: 2–18). Aside from OSA, participants did not suffer from any developmental, psychiatric or neurological disorder, as established in a full neurological examination by a board-certified neurologist.

The control group consisted of 20 healthy subjects and were matched by age, education and sex (average age: 52.40, SD: 15.04, average education: 12.65, SD: 3.56, five female/15 male). The control participants did not suffer from any developmental, psychiatric or neurological disorders and did not have sleeping disorders. All subjects provided signed informed consent agreements and received no financial compensation for their participation. Ethics approval was obtained by Psychology Ethics Committee at University of Szeged, Institute of Psychology.

Tasks

ASRT task

We used the ASRT task in which a stimulus (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 with 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 participants. We emphasized that the aim was to try to respond as quickly and as correctly as possible.

The ASRT consisted of 20 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) was repeated 10 times. Following Nemeth *et al.* (2010) stimuli were presented 120 ms following the previous response. As one block took approximately 1.5 min, the session took approximately 25–30 min. Between blocks, the participants received feedback about their overall RT and accuracy on the screen, and then they had 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, such 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, where numbers represent the four places on the screen, and r represents an event selected randomly from the four possible places), some triplets or runs of three stimuli occur more frequently than others. For example, in the above illustration 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 (Nemeth *et al.*, 2010; Song *et al.*, 2007), we refer to the former as high-frequency triplets and the latter as low-frequency triplets. Of the 64 possible triplets, each 16 high-frequency triplets occur on approximately 4% of the trials, about five times more often than the low-frequency triplets. Note that the final event of high-frequency triplets is therefore more predictable from the initial event compared to the low-frequency triplets (also known as non-adjacent second-order dependency; see Remillard, 2008) (Fig. 1).

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; Song *et al.*, 2007). In addition, general skill learning is revealed in the ASRT task in 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.

To explore how much explicit knowledge participants acquired about the task, we administered a short questionnaire (the same as Song *et al.*, 2007) after the task. This questionnaire included increasingly specific questions such as: 'Have you noticed anything special regarding the task? Have you noticed some regularity in the sequence of stimuli?'. The experimenter rated subjects' answers on a five-item scale, where 1 was 'nothing noticed' and 5 was 'total awareness'. None of the subjects in either the apnea or control groups reported noticing the sequence in the task.

Listening span task

The working memory performance was measured by the listening span task (Daneman and Blennerhassett, 1984). In this test, subjects are required to listen to increasingly longer sequences of sentences and to recall the final word of all the

sentences in each sequence in serial order. A subject's working memory capacity is defined as the longest sequence length at which they are able to recall the final words.

Procedure

We administered the listening span task and ASRT task in one session between 18:00 and 21:00 h in both the OSA and 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 contains blocks 1–5, the second epoch contains blocks 6–10, etc. Subjects' accuracy remained very high throughout the test (average over 96% for both groups), and so we focus on RT for the analyses reported. For RT, we calculated medians for correct responses only, separately 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 considering that it is more or less predictable from the event $n-2$. For the analyses reported below, as in previous research (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 are low-frequency for all participants, and people often show pre-existing response tendencies to them (Howard *et al.*, 2004). By eliminating them, we can ensure that any high- versus low-frequency differences are due to learning and not to pre-existing tendencies.

RESULTS

ASRT analysis

A mixed-design analysis of variance ($_{ANOVA}$) was conducted on the four epochs of the data shown in Fig. 2 with triplet (high versus low) and epoch (1-4) as within-subjects factors, and group (OSA versus control) as between-subjects factors.

There was significant sequence-specific learning (indicated by the significant main effect of triplet: $F_{1,38} = 11.18$, $\eta_p = 0.23$, $P = 0.002$), such that RT was faster on high- than low-frequency triplets. OSA and control groups showed no differences in sequence-specific learning (triplet \times group interaction: $F_{1,38} = 1.21$, $\eta_p = 0.03$, $P = 0.28$).

There was also general skill learning (shown by the significant main effect of epoch: $F_{3,114} = 31.07$, $\eta_p = 0.45$, $P < 0.001$), such that RT decreased across epochs. OSA and control groups performed at the same level (epoch \times group interaction: $F_{3,114} = 0.05$, $\eta_p = 0.001$, $P = 0.98$).

The triplet \times epoch and triplet \times epoch \times group interactions were not significant ($F_{3,114} = 1.60$, $\eta_p = 0.04$, $P = 0.19$; $F_{3,114} = 0.78$, $\eta_p = 0.02$, $P = 0.50$; respectively), indicating that the pattern of learning was similar in the groups. In the

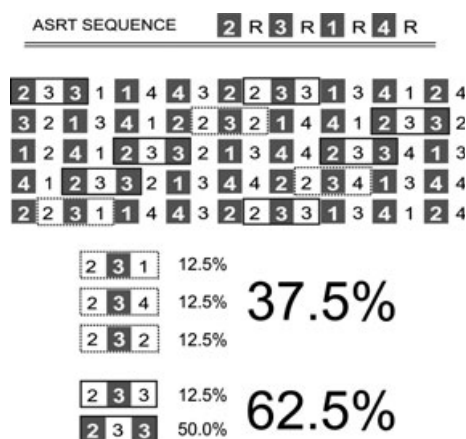


Figure 1. In the alternating serial reaction time (ASRT) task, there are more frequent (high-frequency) and less frequent (low frequency) triplets. In other words, if we know what were the last two elements of the sequence (in this case 2–3–?), there is a 67.5% probability of a certain element as continuation, and only 12.5% probability of all of the other elements.

general RT the OSA group did not differ significantly from the control group; we found only a weak trend (main effect of group: $F_{1,38} = 2.97$, $\eta_p = 0.07$, $P = 0.093$). Because of this slight difference in general RT, we reanalyzed the data using Z-scores and found the same results as in the original analysis, with no differences between the groups regarding sequence-specific and general skill learning (triplet \times group interaction: $F_{1,38} = 0.09$, $P = 0.77$; epoch \times group interaction: $F_{3,114} = 0.20$, $P = 0.89$; triplet \times epoch \times group interaction: $F_{3,114} = 0.92$, $P = 0.92$).

Listening span task

The performance in the Listening span task was analyzed by independent-samples *t*-test. The working memory span of the OSA group was significantly lower (2.55 versus 3.31) compared to the control group ($t_{38} = -4.05$, $P < 0.001$; Fig. 3).

DISCUSSION

Our goal was to investigate whether implicit sequence learning is impaired in OSA. We used the ASRT task, which

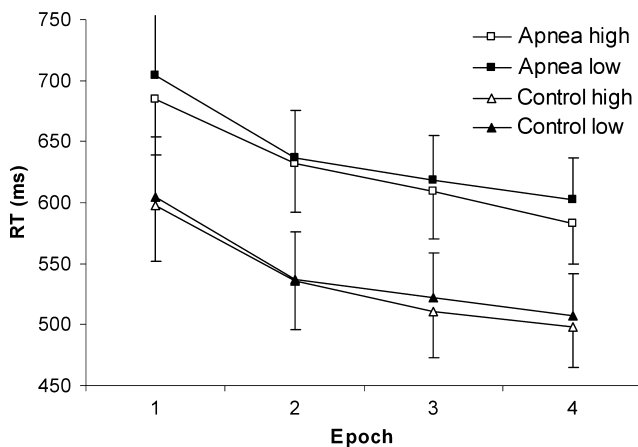


Figure 2. Implicit sequence learning in control and sleep apnea group. Both groups showed general skill learning as well as sequence-specific learning. There were no group differences. Error bars indicate standard error of mean.

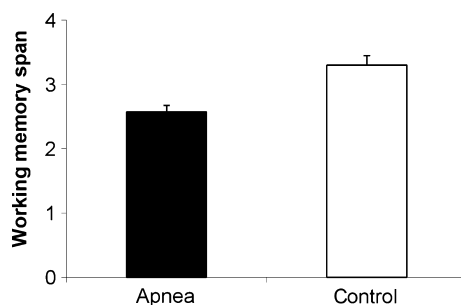


Figure 3. Working memory performance in control and sleep apnea group. The working memory span of the sleep apnea group was significantly lower compared to the control group. Error bars indicate standard error of the mean.

allowed us to differentiate between general skill and sequence-specific learning. We found that OSA patients showed general skill learning and implicit learning of probabilistic sequences similar to that of controls. In contrast, working memory performance measured by listening span task was impaired in the OSA group, consistent with previously reported data. We believe our study to be the first to investigate implicit probabilistic sequence learning in OSA.

Our results on working memory performance are similar to those of earlier studies (e.g. Archbold *et al.*, 2009; Cosentino *et al.*, 2008; Naegele *et al.*, 2006) in 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 (e.g. Cosentino *et al.*, 2008). Thomas *et al.* (2005) also found absence of dorsolateral prefrontal activation during working memory task in patients with OSA.

The intact sequence learning found in this study is similar to several earlier finger-tapping studies (Archbold *et al.*, 2009; Wilde *et al.*, 2007). In contrast to our results, Lojander *et al.* (1999) found impaired learning on a sequence learning task. The nature of the task is critical in the interpretation of the results. To our knowledge, ASRT has never been tested in this patient population. We believe ASRT 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). The ASRT task uses a more complex sequence structure than finger-tapping tasks (probabilistic versus deterministic). On the neuroanatomical level ASRT is associated even more with basal ganglia rather than motor cortex in contrast to the finger-tapping task, where motor cortex plays a critical role in learning performance (Walker *et al.*, 2005).

Our results are in line with sleep deprivation studies. For example, Yoo *et al.* (2007) found that full-night sleep deprivation disrupted formation of new explicit memories. Disruption of slow wave activity (SWA) led to similar results in explicit memory, whereas it did not affect performance on the SRT task (Van Der Werf *et al.*, 2011). This latter result is consistent with Genzel *et al.* (2009), who found that disturbed SWS and rapid eye movement (REM) phases did not impair sequential finger-tapping performance.

According to studies on the relationship between cognitive functions and normal and disrupted sleep (Naegele *et al.*, 2006; Robertson *et al.*, 2004; Song *et al.*, 2007; Stickgold *et al.*, 2002), we suggest that the sleep has a greater impact on the structures related to the more attention-demanding processes than structures involved in less attention-demanding, implicit processes. Our findings support this claim in showing impaired working memory functions versus intact probabilistic sequence learning in OSA. These results are consistent with studies claiming no relationship between these two functions (Feldman *et al.*, 1995; Kaufman *et al.*, 2010; McGeorge *et al.*, 1997; Unsworth and Engle, 2005) and also with Bo *et al.* (2011), who highlight the association between sequence learning and visuospatial working memory compared to verbal working memory examined in our study.

Nevertheless, it is worth mentioning that this study cannot rule out the possible effect of collateral factors such as increasing blood pressure, hormonal changes, weight gain and an increase in diabetes risk, which are often present in OSA patients (Banno and Kryger, 2007). Further investigations are needed to clarify this question.

Taken together, this study found a dissociation between working memory and implicit sequence learning in OSA patients. The working memory showed impairment, while the implicit sequence learning was preserved in spite of the possible hypoxia and sleep restriction in OSA. These results can help us to develop more sophisticated diagnostic tools and more effective rehabilitation programs. Beyond the OSA, our findings complement sleep-dependent memory consolidation models well (Doyon *et al.*, 2009; Robertson, 2009; Stickgold and Walker, 2007), and draw attention the fact that sleep might have less influence on the structures related to implicit processes.

DECLARATIONS OF INTEREST

The authors report no conflict of interest and have no financial disclosures.

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The Consolidation of Implicit Sequence Memory in Obstructive Sleep Apnea

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Abstract

Obstructive Sleep Apnea (OSA) Syndrome is a relatively frequent sleep disorder characterized by disrupted sleep patterns. It is a well-established fact that sleep has beneficial effect on memory consolidation by enhancing neural plasticity. Implicit sequence learning is a prominent component of skill learning. However, the formation and consolidation of this fundamental learning mechanism remains poorly understood in OSA. In the present study we examined the consolidation of different aspects of implicit sequence learning in patients with OSA. We used the Alternating Serial Reaction Time task to measure *general skill learning* and *sequence-specific learning*. There were two sessions: a learning phase and a testing phase, separated by a 10-hour offline period with sleep. Our data showed differences in offline changes of general skill learning between the OSA and control group. The control group demonstrated offline improvement from evening to morning, while the OSA group did not. In contrast, we did not observe differences between the groups in offline changes in sequence-specific learning. Our findings suggest that disrupted sleep in OSA differently affects neural circuits involved in the consolidation of sequence learning.

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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 [1]. Consolidation can be observed as no deterioration of the previously acquired knowledge over the offline period, nevertheless in some cases even offline enhancement can occur. Many studies indicate that sleep contributes to the consolidation of memory traces by enhancing neuronal plasticity [2–6]. Sleep-related enhancement in declarative memory is clearly demonstrated [7–9], but the beneficial effect of sleep on the consolidation of non-declarative (i.e. procedural) knowledge is still controversial. Previous studies that focused on healthy populations found greater improvement in a procedural sequence learning task after a period of sleep than after an equivalent time of wakefulness [10,11]. By contrast, several recent studies failed to find sleep-related improvement in sequence learning [12–15]. The controversial results might be explained by task complexity, for example varying in sequence length and structure. Moreover, some sequence learning tasks used in these studies were unable to separate two aspects of sequence learning, namely general practice-dependent speed-up (so called general skill learning) and sequence-specific learning [10,11,16]. In the

present study, we used the Alternating Serial Reaction Time (ASRT) task [17] to extend previous research by separating and measuring both general skill learning and sequence-specific learning. In this task some runs of three consecutive stimuli (triplets) are more frequent than others. With practice people become faster in responding to these high frequency triplets compared to the low frequency ones, revealing sequence-specific aspects of learning. In contrast, a general speed-up irrespectively of the triplet frequencies is considered to be a result of the general skill aspect of learning in this task [12,14].

Previous studies suggest that sleep disorders (e.g., insomnia) lead to weaker consolidation both of declarative and non-declarative memory [18,19]. One of the most frequent sleep disorders is obstructive sleep apnea (OSA) which is characterized by repeated episodes of upper airway obstruction during sleep, resulting in hypoxia, which leads to repetitive arousals from sleep disturbing normal sleep patterns [20]. Deficits in working memory [21,22], attention, executive functions [23–26], short and long-term verbal and visual memory have been demonstrated in OSA [25,27,28] indicating structural changes in brain circuits crucial for memory [29]. Nevertheless, sequence learning has not been extensively characterized in OSA. Lojander, Kajaste, Maasilta & Partinen [30] have found poor performance in sequence learning in patients with apnea. In contrast, other studies showed intact performance

on a less complex, deterministic sequence learning task [31] and also on a more complex, probabilistic sequence learning task [22], but they found weaker word recall and working memory performance, respectively.

The aforementioned studies investigated on the effect of sleep disorders on learning and memory functions in general but not on the overnight consolidation of the acquired knowledge. Focusing on consolidation, Kloepfer and colleagues [32] examined the memory performance before and after sleep in moderate OSA. They revealed that OSA patients showed reduced declarative (verbal) and non-declarative memory performance after sleep compared to healthy control participants. It is important to note that this study measured non-declarative memory by a motor adaptation task and not by a sequence learning task. To our knowledge, only one study focused on the consolidation of sequence learning in OSA and demonstrated that OSA can negatively affect memory consolidation on a relatively simple motor sequence learning task [16]. Nevertheless, this study used an explicit sequence learning task (fingertapping) with deterministic sequence structures. The aim of the present study was to go beyond previous research in three ways:

- 1) investigating the consolidation processes in OSA by a more complex sequence learning task, namely the sequence structure is not deterministic but probabilistic;
- 2) we use an implicit sequence learning task and not explicit (for example [16]),
- 3) the task used here enables us to separately analyze the consolidation of two aspects of sequence learning, namely general skill and sequence-specific learning.

Based on the previous sleep studies that used implicit probabilistic sequence learning tasks [12,14], our hypothesis is that OSA participants will not show deterioration in sequence-specific and general skill learning over the offline period.

Methods

Participants

Seventeen newly diagnosed, untreated patients with OSA participated in the experiment (average age: 52.41 years, SD: 9.67; average education: 12.65 years, SD: 2.18; 2 females/15 males). OSA was diagnosed by a board-certified sleep-physician based on a full night of clinical polysomnography. The mean Apnea-Hypopnea Index (AHI) was 53.05 events/hour (SD: 23.26 (Range: 21.1–117.3)). Pathological level of AHI was defined as 15 or more per hour [20]. The mean total sleep time (TST) was 330.52 mins (SD: 48.65). Aside from OSA, participants did not suffer from any developmental, psychiatric or neurological disorders as established in a full neurological exam by a board-certified neurologist.

The control group consisted of seventeen healthy participants and was matched by age (average age: 54.24 years, SD: 7.29) and by working memory performance. Working memory capacity was assessed by two widely-used neuropsychological tests: the Backward Digit Span Task (BDST) [33,34] and Listening Span Task (LST) [35,36]. There were no significant differences between the two groups in these tasks (BDST: $t(32) = 1.116$, $p = 0.27$, LST: $t(32) = 0.170$, $p = 0.87$). These criteria were included to eliminate the effect of working memory, as previous studies in healthy participants revealed a relationship between working memory and implicit sequence learning [37,38]. However there is also evidence that the two systems are independent of each other [39–41] (for review see Janacek & Nemeth [42]). Control participants did not

suffer from any developmental, psychiatric or neurological disorders and did not have sleeping disorders. All participants provided signed informed consent and received no financial compensation for their participation. Ethics approval was obtained by the Psychology Ethical Committee at the University of Szeged, Institute of Psychology.

Procedure

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 and 8 PM prior to sleep (Learning Phase) and between 7 and 8 AM after sleep (Testing Phase), thus the average interval between the Learning and Testing Phase was 12 hours. Between the two sessions AHI was measured in a full night of polysomnography in SomnoCenter's sleep lab (Szeged, Hungary). During the data collection, subjects' caffeine and nicotine intake was restricted.

Alternating Serial Reaction Time (ASRT) Task

We used the modified version of the ASRT task in which a stimulus (a picture of a dog's head) appeared in one of four empty circles on the screen [12]. Before beginning the task, detailed instructions were read to participants. They were instructed to press the button corresponding to the stimulus location as quickly and as accurately as possible [12]. The computer was equipped with a special keyboard with four marked keys (Y, C, B and M on a QWERTZ keyboard; thus, compared to the English keyboard layout, the location of the buttons Z and Y were switched), each corresponding to one of the horizontally aligned circles. Session 1 (Learning Phase) consisted of 25 blocks, with 85 key presses in each block – the first five stimuli were random for practice purposes, then an 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) repeated ten times. Similarly to earlier studies [12], stimuli were presented 120-ms after the previous response (response-to-stimulus interval, RSI). Each block required about 1.5 minutes and the entire session took approximately 30–40 minutes. Between blocks, participants received feedback about their overall reaction time and accuracy on the screen and then rested 10 to 20 seconds before starting a new block. Session 2 (Testing Phase) consisted of 5 blocks; the number of key presses and the RSI were the same as in Session 1 and this Testing Phase took approximately 5–10 minutes to complete.

A different ASRT sequence was selected for each participant based on a permutation rule such that each of the six unique permutations of the 4 repeating events occurred. Consequently, six different sequences were used across participants [12].

As there is a fixed sequence in the ASRT alternating with random stimuli (e.g., 2r1r4r3r), some triplets or runs of three consecutive stimuli occur more frequently than others. For example, 2_1, 1_4, 4_3, and 3_2 occur more often because the third element (bold numbers) can be derived from the sequence or can also be a random element (if the sequence is 2r1r4r3r). In contrast, 1_2 or 4_1 occur less often because the third element can only be random. Following previous studies [12,14], we refer to the former as high-frequency triplets and the latter as low-frequency triplets. Out of the 64 possible triplets, each 16 high frequency triplets occur on approximately 4% of the trials, about 5 times more often than the low-frequency triplets. Note that the final event of high-frequency triplets is therefore more predictable from the initial event compared to the low-frequency triplets (also

known as non-adjacent second-order dependency, see in Remillard [43]).

Previous studies have shown that as people practice the ASRT task, they come to respond more quickly to the high-frequency triplets than low-frequency triplets, revealing sequence-specific learning [14,44]. In addition, general skill learning is revealed by the overall speed-up during the practice, irrespectively of the triplet types. Thus, we are able to measure both sequence-specific and general skill learning in the ASRT task.

To explore how much explicit knowledge participants acquired about the task, we administered a short questionnaire (previously used in Song and colleagues [12], Nemeth and colleagues [14]) after the task. This questionnaire included increasingly specific questions such as “Have you noticed anything special regarding the task? Have you noticed some regularity in the sequence of stimuli?” The experimenter rated subjects’ answers on a 5-item scale, where 1 was “Nothing noticed” and 5 was “Total awareness”. None of the participants in either the OSA or control group reported noticing the sequence in the task.

Statistical analysis

To facilitate data processing, the blocks of ASRT were organized into epochs of five blocks. The first epoch contains blocks 1–5, the second epoch contains blocks 6–10, etc. Participants’ accuracy remained very high throughout the test (average >96% for both groups), therefore we focused on reaction time (RT) for the analyses reported. We calculated RT medians for correct responses only (following the standard protocol, see in [12,14,17,44]), separately for high- and low-frequency triplets and for each participant 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 is more or less predictable from the event $n-2$. For the analyses reported below, as in previous research [12,14], 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 show pre-existing response tendencies to them [44]. So by eliminating them we attempted to ensure that any high- versus low-frequency differences were due to learning and not to pre-existing tendencies.

Results

Online learning during Session 1 (Learning Phase)

To investigate learning during Session 1, a mixed design ANOVA was conducted on the first 5 epochs of the data shown in Figure 1A, with TRIPLET (2: high- vs. low-frequency) and EPOCH (5: 1–5) as within-subject factors, and GROUP (OSA vs. control) as a between-subject factor. All significant results are reported together with the η_p^2 effect size and Greenhouse Geisser ϵ correction factors where applicable. Post hoc analyses were conducted by Fisher’s LSD pairwise comparisons.

There was significant sequence-specific learning (indicated by the significant main effect of TRIPLET: $F(1,32)=15.58$, $\eta_p^2=0.32$, $p<.001$), such that RTs were faster on high- than on low-frequency triplets. OSA and control groups showed no differences in sequence-specific learning (TRIPLET×GROUP interaction: $F(1,32)=1.61$, $\eta_p^2=0.04$, $p=0.21$).

There was also significant general skill learning (shown by the significant main effect of EPOCH: $F(4,128)=28.62$, $\eta_p^2=0.47$, $p<.001$), such that RTs decreased across epochs. OSA and control groups performed at the same level (EPOCH×GROUP interaction: $F(4,128)=2.21$, $\eta_p^2=0.06$, $p=0.12$).

The TRIPLET×EPOCH and TRIPLET×EPOCH×GROUP interactions were not significant ($F(4,128)=0.94$, $\eta_p^2=0.03$

$p=0.42$; $F(4,128)=0.48$, $\eta_p^2=0.01$, $p=0.69$; respectively), indicating that the pattern of learning was similar in the groups. In the overall RT, the OSA group differed significantly from the control group, with slower RTs for the OSA group (main effect of GROUP: $F(1,32)=4.95$, $\eta_p^2=0.13$, $p=0.03$). To ensure that this difference in overall RTs did not influence learning measures, we also ran an ANOVA on normalized data (for each participant, the median RTs for high- and low-frequency triplets in each epoch were divided by the overall RT of the first epoch) and found the same results.

Consolidation of sequence-specific and general skill learning

To investigate the offline changes of sequence-specific and general skill learning we compared the RTs from the last epoch of Session 1 (Epoch 5) and the epoch of Session 2 (Epoch 6) in both groups (for similar analyses see [12,14]). These variables were submitted to a mixed design ANOVA with TRIPLET (2: high- vs. low-frequency) and EPOCH (2: last epoch of Session 1 and epoch of Session 2) as within-subject factors, and GROUP (OSA vs. control) as a between-subject factor.

The main effect of TRIPLET was significant ($F(1,32)=32.34$, $\eta_p^2=0.5$, $p<.001$), thus RTs were faster on high- than low-frequency triplets. It was similar in the OSA and control groups (indicated by the non-significant TRIPLET×GROUP interaction: $F(1,32)=1.07$, $\eta_p^2=0.03$, $p=0.31$).

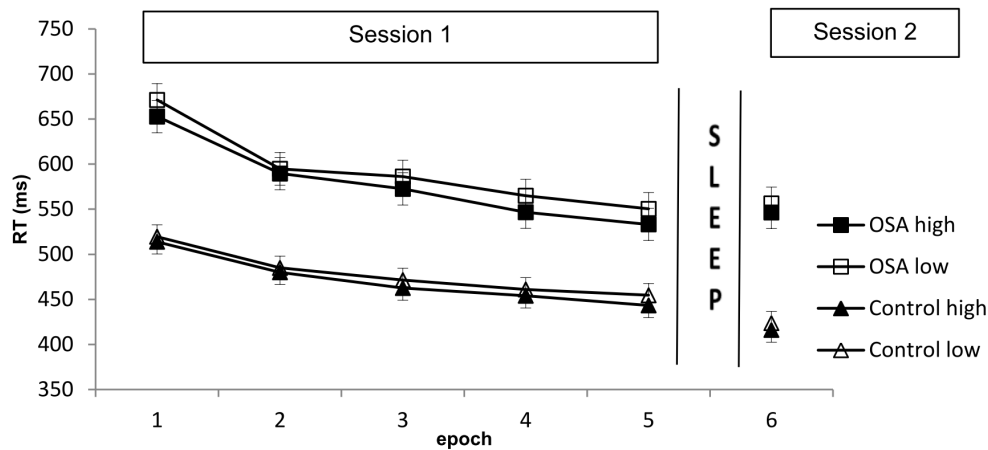
The main effect of EPOCH did not reach significance ($F(1,32)=2.34$, $\eta_p^2=0.07$, $p=0.13$) but the EPOCH×GROUP interaction was significant ($F(1,32)=9.32$, $\eta_p^2=0.22$, $p=0.005$), suggesting that the OSA and control groups showed significant differences in the offline changes of general skills. The LSD post hoc test revealed that the OSA group showed no offline general skill improvement ($p=0.29$), while the control group showed better performance (faster RTs) at the beginning of Session 2 compared to the end of Session 1 ($p=0.003$).

The sequence-specific knowledge did not change significantly during the offline period (TRIPLET×EPOCH interaction: $F(1,32)=2.75$, $\eta_p^2=0.08$, $p=0.11$). The OSA and control groups performed on a similar level (TRIPLET×EPOCH×GROUP interaction: $F(1,32)=0.29$, $\eta_p^2=0.009$, $p=0.59$). The offline changes of sequence-specific and general skill knowledge are shown on Figure 1B–C, respectively.

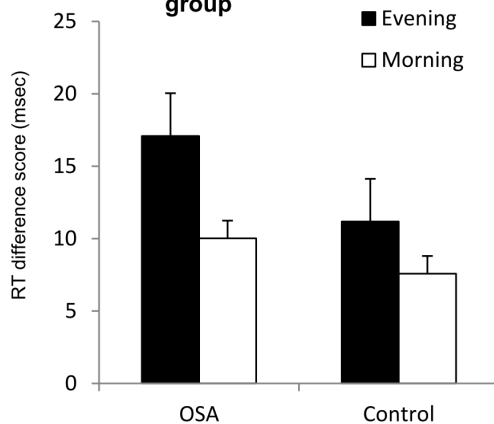
There were significant differences in the general RTs between the OSA and control groups, with slower RTs for the OSA group (main effect of GROUP: $F(1,32)=6.27$, $\eta_p^2=0.16$, $p=0.02$). ANOVA on normalized data revealed the same results, confirming that the significant difference in offline changes of general skills between the OSA and the control group was not due to general RT differences (EPOCH×GROUP interaction: $F(1,32)=11.17$, $\eta_p^2=0.25$, $p=0.002$).

To further confirm the ANOVA results we also analyzed individual differences of sequence-specific and general skill consolidation. In the case of offline sequence-specific changes, we counted the number of participants who exhibited higher sequence-specific learning in Epoch 6 than in Epoch 5 (thus, sequence-specific knowledge in Epoch 6 minus Epoch 5 was above zero, irrespectively of significance testing). A similar number of OSA and control participants (7/17 and 6/17, respectively) showed higher than zero difference in sequence-specific knowledge between Epoch 6 and Epoch 5. Consequently, the number of participants showing the opposite pattern (lower than zero difference between Epoch 6 and Epoch 5) was also similar in the two groups (10/17 and 11/17, respectively). Thus, there was no group difference in sequence-specific consolidation based on

A) Sequence-specific and general skill learning in the OSA and control group in Session 1 and Session 2



B) Offline changes in sequence-specific learning in OSA and control group



C) Offline changes in general skill learning in OSA and control group

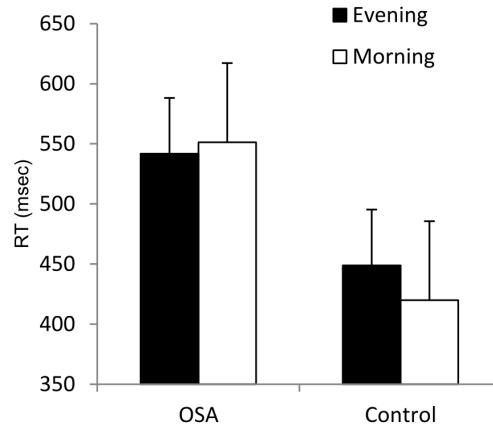


Figure 1. Results of sequence learning and consolidation in the OSA and control group. **A)** Results of sequence-specific and general skill learning in OSA and control group in Session 1 and Session 2: Although the OSA group was generally slower in Session 1, both groups showed significant sequence-specific and general skill learning. There were no differences in learning between the groups; the pattern of learning was similar in the OSA and control groups. **B)** Results of offline changes in sequence-specific learning in OSA and control group: The differences between the low and high frequency triplets indicate sequence-specific learning. There was a decrease in sequence-specific knowledge, such that the learning index of the first epochs of Session 2 was significantly smaller compared to the last epochs of Session 1. There were no significant differences between the OSA and control groups. **C)** The results of offline changes in general skill learning: the differences in overall reaction time between the last epoch of Session 1 and the first epoch of Session 2 regardless of triplet type show general skill learning. There was a trend of improvement in general skill learning. The OSA group showed no offline general skill learning, while the control group showed better performance (smaller RTs) at the beginning of Session 2 compared to the end of Session 1. Error bars indicate SEM. doi:10.1371/journal.pone.0109010.g001

this analysis ($\chi^2(1) = 0.125$, $p = 0.724$) which supports the ANOVA result. In contrast, in the case of general skill consolidation, more controls (14 out of 17) than OSA patients (8 out of 17) showed higher than zero difference in general RTs between Epoch 6 and Epoch 5, thus they were generally faster in Epoch 6 compared to Epoch 5. This group difference in general skill consolidation was significant ($\chi^2(1) = 4.636$, $p = 0.031$) similarly to the ANOVA result.

Discussion

Our goal was to investigate the consolidation of non-declarative learning in OSA. We used a relatively complex sequence learning task that allowed us to differentiate between two components of learning: general skill learning and sequence-specific learning. We found differences in offline changes of general skills between OSA

patients and controls. The control group showed offline improvement from evening (Learning Phase) to morning (Testing phase), 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. We believe our study to be the first to investigate the consolidation of these two aspects of implicit learning by using a task with complex sequence structures in patients with OSA.

In the Learning Phase the OSA and control group showed similar learning patterns in general skill and sequence-specific learning; however the OSA group demonstrated slower RTs in general. These intact learning curves are in line with previous studies investigating non-declarative learning in this patient population [22,30,31]. For example, Nemeth and colleagues [22] and Csabi, Benedek, Janacsek, Katona & Nemeth [45] using

the ASRT task also showed intact sequence learning both in children and elderly adult population with sleep-disordered breathing and OSA. In another type of non-declarative memory, Rouleau, Décary, Chicoine & Montplaisir [46] found preserved learning measured by a sensorimotor adaptation task in OSA patients, although a subgroup of them demonstrated deficits in initial learning performance. This subgroup also had difficulties on other neuropsychological tests (e. g. executive functions). Naegelé et al [25] using the same task also found significant but weaker learning in OSA than in the control group. The authors suggest that patients with OSA have difficulties creating new sensorimotor coordination. In sum, these studies suggest that sensorimotor adaptation might be weaker while the less sensorimotor coordination-demanding sequence learning is intact in OSA.

In the overnight consolidation of non-declarative memory we revealed 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. Kloepper et al [32] found similar results: at the encoding, prior to sleep OSA patients showed similar non-declarative sensorimotor adaptation as the healthy control participants, but they revealed reduced overnight improvement on average RT performance. A recent sequence learning study by Djonlagic et al [16] 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 the case of sequence-specific learning, we found similar performance between the OSA and control groups not only in online sequence-specific learning but also in the consolidation of sequence-specific knowledge. This result is in line with previous studies that failed to find sleep-related changes in the consolidation of sequence-specific learning in healthy participants [12,14]. It suggests that sleep might have less influence on this specific aspect of non-declarative learning. This conclusion is also supported by

two recent reports. Song & Cohen [47] propose that practice and sleep form different aspects of skill. Their results suggest transition learning (as in the ASRT) to be an implicit component of skills that lacks sleep-dependence. In the other recent consolidation study, Meier and Cock [48] found neither deterioration, nor further improvement in sequence-specific learning over the offline period, however, they found offline improvement in general skill learning.

In conclusion, we demonstrated that the offline changes of two components of implicit sequence learning are differentially affected in OSA: in contrast to the preserved consolidation of sequence-specific knowledge, the consolidation of general skills was weaker compared to the controls. Thus, we suggest that long-term sleep disturbances present in OSA play differential role in these two aspects of consolidation in the case of more complex, probabilistic sequences. Nevertheless, a daytime control condition is needed to investigate whether weaker consolidation of general skills is specific to the actual overnight sleep disturbances or to long-term deficits related to sleep disruption. Our findings underscore the importance of examining more specific and focal cognitive functions in OSA. Creating more sophisticated neuropsychological profiles about the cognitive dysfunctions could not only provide clues about which brain networks may be affected in OSA but also can help develop more effective methods of rehabilitation and treatment.

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Author Contributions

Conceived and designed the experiments: EC MVS KJ DN. Performed the experiments: EC. Analyzed the data: EC KJ DN. Contributed reagents/materials/analysis tools: EC KJ DN. Wrote the paper: EC KJ NM DN.

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KÉT HÓNAPOS LÉGSÍNTERÁPIA HATÁSA AZ ALVÁS STRUKTÚRÁJÁRA, A KOGNITÍV FUNKCIÓKRA ÉS A SZORONGÁSRA

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EFFECT OF TWO MONTH POSITIVE AIRWAY PRESSURE THERAPY ON THE STRUCTURE OF SLEEP, COGNITIVE FUNCTION AND ANXIETY

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Az alvási apnoe szindróma során az ismételt hypoxiás epizódok és ennek következtében kialakuló alvászavarok kognitív teljesítményromláshoz vezet. Azt vizsgáltuk, hogy a kezelésére alkalmazott pozitív felső légúti nyomásterápia rövid távon milyen hatással van az alvás struktúrájára, a neuropszichológiai funkciókra és a szorongásra. Ehhez 24 fő (23 férfi, egy nő; átlagéletkor: 53,21 év) obstruktív alvási apnoe szindrómás beteggel vettünk fel emlékezesi teszteseteket a kezelés megkezdése előtt és két és fél hónapos kezelést követően. Az eredmények alapján javulás jelent meg az alvás alatti légzésben, az alvás struktúrájában és a szubjektív aluszékonyságban. A kognitív funkciók tekintetében a kezelés pozitív hatással volt a szorongás szintjére, a komplex munkamemória és a rövid, valamint hosszú távú verbális emlékezesi teljesítményre, tehát elsősorban azokban a feladatokban jelent meg javulás, amelyek több agyterület összehangolt működését igénylik. Ennek alapján feltételezhető, hogy a légszínterápiás kezelés már rövid távon javulást eredményez az alvás architektúrájában, illetve, hogy az alvási apnoe következtében kialakuló dementia bizonyos funkciókat tekintve reverzibilis.

Kulcsszavak: hypoxia, alvászavarok, obstruktív alvási apnoe szindróma, pozitív felső légúti nyomás, munkamemória, végrehajtó funkciók, szorongás, kognitív funkciók

Obstructive sleep apnea is a common disorder, characterized by repeated episodes of upper airway obstruction during sleep, resulting in intermittent hypoxia and disruption of the normal sleep pattern, which caused cognitive dysfunction in these patients. Nasal continuous positive airway pressure is the treatment of choice for this disorder. The aim of the study is to evaluate the effect of short-term positive airway pressure on sleep pattern (polysomnographic measures), cognitive function and anxiety. Twenty four newly diagnosed and previously untreated patients with obstructive sleep apnea were evaluated a battery of neuropsychological tests before and after 2 and a half months of the treatment. We focused on working memory, short and long-term episodic memory, executive functions, anxiety and subjective sleepiness. Our results showed that the two and half month of treatment improved the respiration during sleep, sleep pattern and the subjective sleepiness. We found improvement in short- and long-term verbal memory, and complex working memory. Despite of treatment we did not find improvement in visuospatial learning. These results reveal that 2 and a half months of positive airway pressure treatment restored not only the normal respiration during sleep and normal sleep pattern, but also the cognitive functions. Our study suggests that cognitive dysfunction is at least partial reversible in obstructive sleep apnea patients after positive airway pressure treatment.

Keywords: hypoxia, sleep disruption, obstructive sleep apnea syndrome, positive airway pressure, working memory, executive function, anxiety, cognitive functions

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Az obstruktív alvási apnoe szindróma az Alvászavarok Nemzetközi Osztályozása alapján az alvásfüggő légzésvizsgálatok csoportjába tartozik¹. Előfordulási gyakorisága a nyugati társadalmakban megközelítőleg 5%, nagyobb arányban jelenik meg az afroamerikai és az ázsiai populációban, illetve a férfiak és az idősebb korosztály körében^{2,3}. Az éjszakai alvás során ismétlődően fellépő hypoxiás epizódokat a felső légút elzáródása okozza, melynek legfontosabb kockázati tényezői az obesitas, illetve bármilyen anatómiai elváltozás, ami növeli a felső légutak összeomlásának veszélyét (például tonsillahypertrophia, macroglossia, retrognathia, a garat lágy részeinek hyperplasiája, mandibularis maxillaris hypoplasia vagy valamilyen nasalis obstrukció). A dohányzás, az alkoholfogyasztás, a szedatívumok és hipnotikumok szedése tovább növelheti kialakulásának esélyét^{2,4,5}.

Az abnormális légzés meghatározásának legfontosabb paraméterei az apnoe-hypopnoe index (AHI), az ébredést kiváltó légzési erő (RERA-Respiratory Effort-Related Arousal) és a légzésvizsgálatindex (RDI-Respiratory Disturbance Index), melyek kritériumait az **1. táblázatban** foglaltuk össze^{2,6,7}.

Az American Academy of Sleep Medicine az obstruktív alvási apnoe súlyosságát az apnoe-hypopnoe index és az aluszékonyság alapján határozza meg. Ez a két diagnosztikai faktor nem feltétlenül jár együtt. Ennek értelmében megkülönböztünk enyhe, mérsékelt és súlyos alkategóriákat. Enyhe esetben nappal akaratlan álomosság és önkéntelen alvási epizódok jelennek meg, olyan kis figyelmet igénylő feladatokban, mint a tévézés vagy olvasás, az AHI 5–15/óra. Mérsékelt esetben már nagyobb figyelmet igénylő feladatokban is bekövetkezik önkéntelen elalvás, például koncertek, találkozók alatt, az AHI 15–30/óra. Súlyos esetben pedig már vezetés, étkezés vagy beszélgetés közben is felléphetnek alvási epizódok, az AHI meghaladja

a 30/órát^{1,2}. Az éjszakai apnoés események következtében kialakuló tüneteket fel lehet osztani nappal és éjszaka megjelenő szimptomákra, melyeket a **2. táblázatban** foglaltunk össze. Nemenként eltérnek a tünetek, férfiakra inkább az észlelhető apnoe, a fuldoklás, zihálás és a horkolás jellemző, a nőkre pedig a depresszió és a reggeli fejfájás^{2,3,6}.

Patomechanizmusát tekintve a felső légút elzáródása hypoxiás állapotot vált ki, melyet az agytörzsi kemoreceptorok érzékelnek és ébredési folyamatot indítanak el. A szimpatikus aktivitás növekedése és az erőltetett légzés végül az esetek többségében nem tudatosuló ébredéshez vezet, akár több százszor is az éjszaka folyamán. Ez az ébredés a szervezet védekező mechanizmusa, védi az agyi struktúrákat a hypoxia által okozott károsodásoktól, akár más szervrendszerek megterhelésével is, olyan következményeket idézve ezzel elő, mint a hipertenzió, az arrhythmia, a szívinfarktus vagy a stroke^{8,9}.

A krónikus betegségek kialakulása mellett a betegek 75%-ában mutattak ki kognitív teljesítményromlást², ami elsősorban olyan funkciókat érint, mint a figyelem^{10–14}, a végrehajtó funkciók^{10, 15, 16}, a motoros kivitelezés^{17, 18}, valamint a rövid és hosszú távú verbális és vizuális emlékezeti teljesítmény^{16, 19, 20}. Ezeknek a területeknek a károsodása egyes eredmények szerint összefüggést mutat az alvási apnoe súlyosságával^{10, 21}. Vitatott kérdés, hogy a hypoxia vagy az alvásképződés áll a tünetek hátterében. Egyes szerzők a hypoxiának tulajdonítják a károsodást, ami elsősorban a frontális és temporális területekre hat, felborítja a központi idegrendszer hemodinamikai státusát és megakadályozza a neurotranszmitter-szintézist^{18, 22–24}. Mások a fragmentált alvást hangsúlyozzák, melynek során elsősorban a NREM 3. és NREM 4. stádiumok, tehát a mélyalvás, illetve a REM-alvásfázis csökken és megnő a felületes NREM 1. és NREM 2. stádiumokban eltöltött idő. Ebből adódóan a betegek csak szenderegnek, nem jutnak el a mély alvásstádium-

1. táblázat. Az abnormális légzés meghatározásának legfontosabb paraméterei^{2,6,7}

Apnoe (AI)	A légzés teljes megszűnése vagy legalább 90%-os csökkenése, amely megnövekedett légzési erővel és 2–4%-os oxigénszaturáció-csökkenéssel jár, és legalább 10 másodpercig fennáll.
Hypopnoe (HY)	A légzés legalább 50%-os csökkenése, amely 4%-os oxigéndeszaturációval és megnövekedett légzési erővel jár, és legalább 10 másodpercig fennáll.
Apnoe-hypopnoe index (AHI)	Apnoe- és hypopnoe-események előfordulása alvásóránként.
Ébredést kiváltó légzési erő (RERA)	Megnövekedett légzési erő, ami ébredést eredményez, de még nem felel meg az apnoe és a hypopnoe kritériumának.
Légzésvizsgálatindex (RDI)	Apnoék, hypopnoék és az ébredést kiváltó légzési erő együttes száma alvásóránként.

mokba, ami elsősorban a frontális területek pihenését szolgálja. Ennek hiányát a napközben megnyilvánuló aluszékonyosság jelzi, ami önmagában is ronthatja a teljesítményt^{25–28}. Emellett alvás alatt is történik emlékezeti megszilárdulás, melynek során a nappal szerzett információk frissítése és feldolgozása történik a hippocampus és a kéreg közötti információáramlás révén. Ehhez a NREM és a REM alvófázisokra egyaránt szükség van, viszont a nem megfelelő alvási architektúra megakadályozhatja ezt a konszolidációs folyamatot^{29–33}. PET-vizsgálatok alapján úgy tűnik, hogy az alvásdepriváció hatására elsősorban a thalamus, a prefrontális és a posterior parietalis területeken csökken az aktivitás²⁷. Illetve vannak kutatási eredmények, melyek szerint a hypoxia és az alvásdepriváció egyaránt szerepet játszik a diszfunkció kialakulásában, a hypoxia elsősorban a végrehajtó funkciókra és a motoros kivitelezésre hat, a normális alvásstruktúra felborulása pedig a figyelmi és emlékezeti funkciókban okoz deficitet^{7, 18, 34–36}.

Az obstruktív alvási apnoe szindróma kezelésére többféle módszer létezik, ezek közül az egyik leghatékonyabb a pozitív felső légúti nyomásterápia, ami a be- és kilégzés alatt folyamatos pozitív nyomás biztosításával csökkenti a légzési munkát és megakadályozza a felső légutak összeomlását³⁷. Az alvásmintázatra és az alvás alatti légzésre gyakorolt hatásával kapcsolatban a kutatások többsége már egy éjszakás használatot követően jelentős javulást talált az alvás hatékonyságában. Csökken a felületes alvástádiumokban eltöltött idő, az alvás alatti ébredések száma és az apnoés események előfordulása, ezzel szemben pedig nő az oxigénszaturáció, a mélyalvás és a REM aránya, valamint a teljes alvásidő^{25, 26, 28, 36, 38–40}. A neuropszichológiai funkciókra és a pszichés státusra gyakorolt hatásával kapcsolatban ellentmondásosak a kutatási eredmények. Egyes szerzők a kezelés ellenére nem találtak javulást a kognitív funkciókban vagy az érzelmi státusban^{41–45}. Ezzel szemben mások szerint a fragmentált alvás által okozott tünetek visszafordíthatóak, javulást találtak a verbális és téri-vizuális emlékezeti teljesítményben⁴⁶, illetve a figyelmi folyamatokat mérő teszteken és az éberségben, csökkent a tévesztések és a lapsusok száma, valamint a reakcióidő^{7, 47, 48, 49}. A készülék használati idejével kapcsolatban *Zimmermann* és munkatársai⁵⁰ három hónapot követően nagyobb mértékű javulást találtak a verbális emlékezetben azok esetében, akik négy óránál többet használták a készüléket éjszakánként,

2. táblázat. Az obstruktív alvási apnoe szindrómához társuló tünetek^{2, 4, 5}

Éjszakai tünetek	Nappali tünetek
Hálótárs által észlelt apnoe (>5 db/óra)	Napközbeni aluszékonyosság
Nem pihentető alvás	Koncentrációzavar
Gyakori ébredés zihálás, fuldoklás kíséretében	Kognitív deficit
Fenyegető, nyugtalanító álmok	Reggeli fejfájás
Horkolás	Szájszárazság
Verejtékezés, nyáladzás	Hangulatváltozás
Nocturia	Csökkent libido, impotencia

azokhoz képest, akik ennél kevesebbet használták, akárcsak *Felver-Grant* és munkatársai⁵¹, akik ugyanennyi idejű kezelést követően a munkamemóriában mutattak ki jobb teljesítményt, habár a motoros kivitelezést és a végrehajtó funkciókat mérő teszteken az optimális készülékhasználat ellenére is a károsodott tartományban maradtak az eredmények. Szerintük a hypoxia olyan mértékű strukturális károsodást okoz, elsősorban a frontális területekhez kapcsolódó magasabb szintű végrehajtó funkciókban, ami már nem reverzibilis^{7, 18, 27, 34, 47–49}. Ezért kutatásunk célja annak megállapítása, hogy rövid távú (két és fél hónapos) pozitív felső légúti nyomásterápia milyen hatással van az alvás minőségére, a kognitív funkciókra és a szorongás mértékére.

Módszer

RÉSZTVEVŐK

A vizsgálatban összesen 24 fő (23 férfi, egy balkezes/23 jobbkezes) vett részt, átlagéletkoruk 53,21 év (szórás: 12,11), az iskolában töltött évek átlaga 12,17 (szórás: 2,20). Az apnoe hypopnoe index (AHI-index) alapján három fő enyhe, öt fő közepesen súlyos és 16 fő súlyos apnoés beteg alkotta a mintát, az AHI-index átlagértéke az összes vizsgálati személy esetében a kezelés előtt: 54,078/óra (szórás: 31,72). Kizárólag azokat választottuk ki, akik esetében az első diagnosztikára szolgáló éjszaka alatt, a polyszomnográfiai mérés alapján alvási apnoe szindrómát diagnosztizáltunk. Közülük 16-an CPAP-, nyolcan BIPAP-készüléket kaptak. A két tesztfelvétel között eltelt idő alatt, ami átlagosan két és fél hónap volt, a vizsgált személyek átlagosan 370 órát használták a készüléket. A légszínterápia megkezdése előtt és a két hónapos kontrollvizsgálaton is felmértük a szubjektív aluszékonytságot az Epworth Aluszékonyossági Skálával. Két hónapos készülékhasználatot követően szignifikáns javulást találtunk a szubjektív aluszékonyosság mértékében [t(19)=4,250, p<0,001]. A vizsgált személyek vala-

mennyien az SZTE, Szent-Györgyi Albert Klinikai Központ, Somnocenter, Dél-alföldi Regionális Alvásdiagnosztikai Terápiás Centrum, Szeged beteganyagából kerültek ki. A tesztfelvétel előtt minden résztvevőt részletesen informáltunk a kutatás céljáról és menetéről, valamint írásbeli beleegyezést is kértünk. A vizsgálat során betartottuk a Magyar Pszichológiai Társaság által előírt etikai szabályokat.

VIZSGÁLATI ESZKÖZÖK

Poliszomnográfia

Az éjszakai alvásvizsgálathoz standard poliszomnográfát alkalmaztunk, melynek során rögzítettük az agyi elektromos tevékenységet (EEG), a szív működést (EKG), a szemmozgásokat (EOG), és az izomaktivitást (EMG). A poliszomnográfia mellett az alvás alatti mozgások detektálására aktigráfias vizsgálat is történt. Emellett megfigyeltük a légzésdinamikát (orr- és szájlégzés, hasi és mellkasi légzés) és a vér oxigénszaturációját (Profox). Infrakamerával videofelvétel készült az alvás alatti pozícióváltásokról, mikrofonnal hangfelvétel az alvás alatti hangjelenségekről. Az alvásstádiumok meghatározására, valamint a fiziológiai változások követésére a *Rechtschaffen, Kales*⁵² által meghatározott kategóriákat vettük figyelembe. Az alváskutatás és az alvás- és emlékezeti konszolidációra vonatkozó szakirodalom alapján a legfontosabb változókat, amiket mi is kiemelten kezeltünk a vizsgálat során, a **3. táblázatban** foglaltuk össze^{7, 47, 48, 53–56}.

A kognitív funkciók mérőeljárásai

A verbális rövid távú emlékezet mérőeljárásai

Számterjedelemteszt – a vizsgálati személynek mindig egy elemmel bővülő számsorozatot kell visszamondania azonos sorrendben. Minden terjedelemhez négy sorozat tartozik, amit a vizsgálat vezetőjének egyenként kell felolvasnia egy másodperces szünetet hagyva közöttük. A legkevesebb sorozat három, a legtöbb kilenc számot tartalmaz. Csak az a számsorozat fogadható el, amit a vizsgált személy pontosan megismétel, a felcserélés vagy kihagyás hibának számít. Ha legalább két sorozatot megismétel, akkor lehet továbblépni a következő, eggyel nagyobb terjedelemre. A vizsgált személy rövid távú emlékezeti terjedelmét az a sorozathosszúság jelöli, amiből legalább kettőt helyesen viszsza tud mondani^{57–59}.

Álszóismétlési teszt – a vizsgálati személynek egyre hosszabb értelmetlen szavakat kell megismételnie. A feladat összesen harminchat szóból áll, a

legrövidebb egy, a leghosszabb kilenc szótagú. Mindegyik szóhosszúsághoz négy álszó tartozik, melyből legalább kettőt kell megismételni, hogy továbblépjen a következő sorozatra. A vizsgált személy álszóterjedelmét az a szótaghosszúság fogja jelölni, amiből legalább kettőt helyesen meg tud ismételni^{57–60}.

A komplex munkamemória mérőeljárásai

Hallási mondatterjedelem teszt – a vizsgált személynek el kell döntenie a hallott mondatokról, hogy igaz vagy hamis állítások, és meg kell jegyeznie minden mondat utolsó szavát. Egy blokkon belül a mondatok száma kettőtől nyolcig terjed. Az adott blokk mondatainak elhangzása után vissza kell mondani a megjegyzett szavakat helyes sorrendben, csak ezután lehet áttérni a következő blokkra. A teszt végső eredményét a három blokk átlaga adja^{61, 62}.

Fordított számterjedelem teszt – akárcsak a számterjedelem tesztnél, az egyes terjedelmekhez négy számsorozat tartozik, melyeket a vizsgálat vezetőjének egyenként, egy másodperces szünetet hagyva kell felolvasnia, a vizsgált személynek viszont fordított sorrendben kell megismételnie. A következő sorozat megkezdésének feltétele az előző sorozatból legalább két számsorozat hibátlan visszamondása. A személy komplex munkamemória-terjedelmét az a sorozathosszúság adja, amiből legalább kettőt helyesen meg tud ismételni^{59, 63}.

A téri-vizuális rövid távú emlékezet mérőeljárásai

Corsi-kockák teszt – a vizsgált személynek egy fekete táblán, kilenc darab szabálytalanul rögzített, körülbelül 2 cm átmérőjű, szintén fekete kockát kell ugyanabban a sorrendben visszamutatnia, mint ahogy a vizsgálat vezetője mutatta korábban. A legelső sorozat kettő, a legutolsó kilenc kocka megismétléséből áll. Legalább két sorozatot kell helyesen visszamutatni, hogy a következő, eggyel magasabb blokkba léphessen. A téri-vizuális rövid távú emlékezet terjedelmét az a sorozathosszúság fogja jelölni, amit a vizsgált személy helyesen viszsza tud mutatni^{59, 63}.

A végrehajtó funkciók mérőeljárásai

Betűfluencia – a vizsgált személynek egy percig kell bizonyos hanggal kezdődő szavakat felsorolni úgy, hogy ne legyen közöttük személyes névmás, szám vagy ugyanannak a szónak ragozott és képzett alakja^{59, 64}. Vizsgálatunkban az első alkalommal „k” és „t”, a második alkalommal „m” és „s” hanggal kellett szavakat felsorolni.

Szemantikus fluencia – ugyancsak egy perc alatt bizonyos kategóriákba tartozó szavakat kell felsorolni.

3. táblázat. A vizsgálatban használt legfontosabb alvásváltozók^{7, 47, 48, 53–56}

Alvásváltozók	Rövidítések	Jelmagyarázat
Ágyban töltött idő (Time In bed)	TIB	A villanyoltástól a reggeli felkelésig eltelt idő (percekben)
Teljes alvásidő (Total Sleep Time)	TST	Az alvástádiumok összejeje, kivéve az ébredéseket/tényleges alvásidő (percekben)
Alvásperiódus-idő (Sleep Period Time)	SPT	Alvásidő az elalvástól az utolsó ébredésig (percekben)
Alváskezdet-latencia (Simple Sleep Onset Latency)	SSL	Elalváshoz szükséges idő (percekben)
Ébrenlét alvás alatt	WK	Alvásidő – tényleges alvásidő (percekben)
Összes ébrenlét (Time in Wake)	TWK	Ébrenlétek összessége (percekben)
Alváshatékonysági index (Sleep Efficiency)	SE	Teljes alvásidő × 100 / ágyban töltött idő
Időtartam		Az egyes alvásfázisok és stádiumok hossza (percekben)
Horkolás		Az egyes alvásfázisokban és stádiumokban megjelenő horkolások száma (darab/óra)
Lassú hullámú alvásfázis (Non-Rapid Eye Movement)	NREM	Lassú hullámú, gyors szemmozgás nélküli, az éjszaka első felében domináló alvásfázis
NREM 1. stádium	S1	Szendergés, lassú hullámú szemmozgás, magas frekvenciájú, alacsony amplitúdójú hullámok túlsúlya (β- és θ-hullámok)
NREM 2. stádium	S2	Felületes alvás, alacsony feszültségű θ-θ-hullámok, K-komplexusok és alvási orsók megjelenési helye
NREM 3. stádium	S3	Középmély alvás, lassú δ-hullámok, szemmozgás teljes hiánya
NREM 4. stádium	S4	Mélyalvás, δ-hullámok 50%-os túlsúlya
Mélyalvás	SWS	NREM 3. és NREM 4. stádium
Gyors szemmozgásos alvásfázis (Rapid Eye Movement)	REM	Gyors szemmozgásos, deszinkronizált EEG-vel jellemzett alvásfázis, mely az éjszaka második felében dominál (α-, β-, θ-hullámok)
Gyors szemmozgás (Rapid Eye Movement)	REM	Gyors szemmozgás, mely elsősorban a REM-alvásfázisban dominál
Lassú szemmozgás (Slow Eye Movement)	SEM	Lassú szemmozgás, mely elsősorban a NREM 1. stádiumban dominál
α-hullám (α Waves)		Éber, nyugalmi állapotot jelző 8–12Hz-es hullám
Δ-hullám (Δ Waves)		0,5–4 Hz közötti lassú hullám, mely a mély alvás jele, legkifejezettebben a frontális régióban jelenik meg
Alvási orsók (Sleep Spindles)		12–16-Hz-es növekvő, majd csökkenő amplitúdójú (bifázisos) hullámok, melyek a thalamusban képződnek, a thalamus és a kéreg közti információáramlást jelzik
Apnoe-hypopnoe index (Apnea-hypopnea Index)	AHI-index	Apnoék és hypopnoék előfordulása alvásóránként, (százalékban)
Apnoe-hypopnoe esemény	AHI-esemény	Apnoék és hypopnoék előfordulása alvásóránként (darabszámban)
Apnoe-hypopnoe átlagidő	AHI-átlagidő	Apnoék és hypopnoék együttes átlagideje, (másodpercben)
Légzészavarindex (Respiratory Disturbance Index)	RDI TST	Apnoék, hypopnoék és az ébredést kiváltó légzési erő (RERA) alvásóránként a teljes alvásidő alatt
Légzészavarindex NREM-ben	RDI NREM	Apnoék, hypopnoék és az ébredést kiváltó légzési erő (RERA) alvásóránként NREM-ben
Légzészavarindex REM-ben	RDI REM	Apnoék, hypopnoék és az ébredést kiváltó légzési erő (RERA) alvásóránként REM-ben

3. táblázat. Folytatás

Alvászváltozók	Rövidítések	Jelmagyarázat
Legkisebb szaturáció (Minimum Oxygen Saturation)	min SaO ₂	Az artériás vér oxigéntelítettségének legalacsonyabb értéke (százalékban)
Átlagszaturáció (Mean Oxygen Saturation)	mean SaO ₂	Az artériás vér oxigéntelítettségének átlagértéke (százalékban)
Oxigéndeszaturációs index (Oxygen Desaturation Index)	ODI	Az oxigénszaturáció normálszintjétől (90-95%) való legalább 4%-os csökkenés alvászóránként (százalékban)

rolniuk a vizsgálati személyeknek. Az eredményt mindkét fluenciafeladat esetében a helyesen felsorolt szavak száma adja, a helytelen szavak vagy az ismétlés hibának számít^{59, 64}. Az adatfelvétel során első alkalommal „állat”, másodsorra „élelmiszert-boltban kapható termékek” felsorolását kértük.

A hosszú távú verbális, vizuális és epizodikus emlékezet mérőeljárása

Rivermead Viselkedéses Emlékezeti Teszt – eredetileg 11 feladtból áll, melyből négy részfeladat használtunk fel, a kereszt- és vezetéknev, a tárgyképek és a történetek azonnali és késleltetett felidézését. A kereszt- és vezetéknevre emlékezés során egy portrén lévő személy teljes nevét kell megismételnie a vizsgált személynek azonnal és rövid késleltetést követően. Mindkét esetben a helyes válasz 2 pontot ér, ha csak a vezeték- vagy a keresztnev helyes, akkor 1 pont jár, ha nem emlékszik a névre vagy helytelen nevet mond, akkor 0 pont. A tárgyképekre emlékezésnél 10 darab, tárgyat ábrázoló képet mutat a vizsgálat vezetője, amit a vizsgált személynek meg kell neveznie. Ezt követően azonnal, majd feladattal kitöltött késleltetést követően 20 darab kép közül kell kiválasztania, hogy melyik 10-et látta korábban. Összesen 10 pontot lehet elérni, minden helyes megoldás 1 pontot ér. A történetre emlékezésnél a vizsgálat vezetője által felolvasott történetből kell minél több részletet visszaidézni közvetlenül a felolvasás után, majd késleltetve. A történet 21 elemre tagolódik, ennek megfelelően 21 pontot lehet elérni, minden helyesen megismélt elem 1 pontot ér, ha csak részben jó a megoldás, akkor fél pont jár^{65, 66}.

A szorongás mérésére alkalmazott mérőeljárás

Spielberger-féle Állapot-Vonás Szorongás Kérdőív – a vizsgálati személynek negyven állításról kell eldöntenie, hogy milyen mértékű szorongás jellemzi az adott pillanatban (állapotszorongás), illetve általában (vonásszorongás). Az állításokat egytől né-

gyig terjedő skálán lehet pontozni. Az értékelésnél összegződnek az adott pontok, egyes tételeknél fordított pontszámokkal kell számolni. A végeredményt az összes mondatra adott pontok és fordított pontok számának összege adja. Mindkét részteszten minimum 20, maximum 80 pontot lehet elérni. Az első húsz állítás az állapotsszorongás értékét mutatja. Nemenként eltérnek az átlagok, a férfiak esetében 38,40 (szórás: 10,66), a nők esetében 42,64 (szórás: 10,79). Huszonegytől 40-ig az állítások a vonásszorongást mérik, ahol a férfiak átlaga 40,96 (szórás: 7,78), a nőké 45,37 (szórás: 7,97)^{67, 68}.

Egyéb alkalmazott mérőeljárások

Epworth Aluszékonysági Skála – a vizsgálati személynek nyolc jellemző élethelyzetben kell értékelni az elalvási hajlamot. Összesen 24 pontot lehet elérni, 10-től tekinthető kórosnak az aluszékonyság⁶⁹.

ELJÁRÁS

A vizsgálatot az SZTE, Szent-Györgyi Albert Klinikai Központ, Somnocenter, Szeged, Dél-alföldi Regionális Alvásdiagnosztikai és Terápiás Centrumban végeztük. A résztvevők kizárólag olyan személyek voltak, akik esetében alvási apnoe szindrómát diagnosztizáltak és kezelésükre légszínterápiát írtak elő. A neuropszichológiai tesztek felvételére két alkalommal került sor, először a titrálást megelőzően, majd két és fél hónapos készülékhasználatot követően, amikor kontrollvizsgálatra jöttek vissza. Titrálás során először a legalacsonyabb nyomáson (2–5 vízcml) kell aludni a vizsgált személynek, hogy megjelenjenek a rá jellemző tünetek, majd lassan emelik a nyomást, amíg az apnoék, végül a horkolás is eltűnik, rendeződik a légzés, a szívfrekvencia és az oxigénszaturáció. Az optimális nyomásérték az a minimumnyomás, ami eltünteti az apnoékat és a hypopnoékat⁴. Mindkét tesztfelvétel alkalmával a vizsgálati személyek este 19.00 órára értek be az alváslaborba, a tesztfelvétel körülbelül 19.00 és 20.00

óra között zajlott, a villanyoltásra 22.00 órákor került sor. Ahol lehetett, a két hónapos kontrollvizsgálatkor más példákat alkalmaztunk a teszteknél az ismétlési hatás elkerülésére. A tesztek felvétele véletlenszerűen történt a fáradási hatás kiküszöbölésére, illetve amennyiben igényelték a vizsgált személyek, szünetet tartottunk a tesztek felvétele között.

STATISZTIKAI ANALÍZIS

A felvett adatok elemzéséhez az SPSS 15.0 statisztikai programcsomagot használtuk, a kezelés előtti és utáni kognitív funkciók, szorongásszint, valamint az alvási paraméterek összevetése párosított t-próbával történt, az egyes összefüggések vizsgálatára pedig korrelációs számításokat (Pearson) végeztünk.

Eredmények

A POLISZOMNOGRÁFIÁVAL MÉRT ALVÁSMUTATÓK VÁLTOZÁSA

Diagnosztikai fázis alatti adatfelvétel (1. alkalom) és a titrálás alatti adatfelvétel (2. alkalom) összehasonlítása

Alvásstruktúra

Az első mérésen, a diagnosztikai éjszakai és a második mérésen, a titráláson, ahol már készülékekkel aludtak a vizsgált személyek, az alvászváltozók eredményei közül szignifikánsan csökkent az alvás alatti ébrenlét (WK) [t(14)=-3,192, p=0,007] és az ébrenlétek összességükben (TWK) [t(14)=3,640, p=0,003]. Ennek hatására, szignifikánsan növekedett a teljes alvásidő (TST) [t(14)=-3,192, p=0,007], a mélyalvás mennyisége (SWS) [t(14)=-5,660, p<0,001] és a REM-fázis [t(14)=-3,165, p=0,007], illetve javult az alvászhatékonysági index [t(14)=-3,478, p=0,004]. Az NREM 1. stádium (S1 TST) mennyisége a teljes alvásidőhöz képest szignifikánsan csökkent [t(14)=3,659, p=0,003]. Csökkent az itt megjelenő α -hullámok mennyisége (S1- α) [t(14)=2,329, p=0,035] és tendenciaszerűen csökkent a δ -hullámok megjelenése (S1 δ) [t(14)=1,822, p=0,90] is. Szignifikáns csökkenés jelent meg a második alvászstádium ágyban töltött idejében (S2 TIB) [t(14)=2,544, p=0,023], az itt megjelenő δ -hullámok mennyiségében (S2 δ) [t(14)=2,290, p=0,038] és a horkolásban (S2 horkolás) [t(14)=2,928, p=0,011]. Tendenciózus csökkenést regisztráltunk a NREM 2. stádium alvásperiódus idejében (S2 SPT) [t(14)=3,268, p=0,006] és a lassú szemmozgásban (S2 SEM) [t(14)=1,776, p=0,097]. A NREM 3. stádiumban folytatódott a csökkenő tendencia, szigni-

fikáns csökkenést mutatott az itt megjelenő gyors szemmozgás (S3 REM) [t(14)=-2,204, p=0,045] és a horkolás (S3 horkolás) [t(14)=2,455, p=0,028]. A korábbi alvászstádiumok csökkenésével ellentétben, szignifikánsan növekedett a NREM 4. stádium időtartama (S4 időtartam) [t(14)=-3,617, p=0,003], az alvásperiódus ideje (S4 SPT) [t(14)=-4,715, p<0,001] és az ágyban töltött idő (S4 TIB) [t(14)=-4,647, p<0,001]. A teljes alvásidőhöz képest tendenciaszinten nőtt a NREM 4. stádiumban eltöltött idő is a teljes alvásidőhöz képest (S4 TST) [t(14)=-3,281, p=0,005]. Jelentősen nőtt az itt megjelenő δ -hullámok (S4 δ) [t(14)=-2,394, p=0,031], lassú (S4 SEM) [t(14)=-2,177, p=0,047] és gyors szemmozgások (S4 REM) [t(14)=-2,224, p=0,043] aránya.

Alvás alatti légzési események

Titrálás során a CPAP/BIPAP készülékek használata szignifikánsan javította a légzéscsavarindexet a teljes alvásidő alatt (RDI TST) [t(15)=7,220, p<0,001], illetve a NREM (RDI NREM) [t(14)=6,798, p<0,001] és a REM (RDI REM) szakaszokban regisztrált légzéscsavarindexet [t(14)=8,341, p<0,001]. Jelentősen csökkent az apnoe-hypopnoe óránkénti előfordulási aránya (AHI-index) [t(22)=6,687, p<0,001], így a darabszáma is (AHI-esemény) [t(22)=7,961, p<0,001], illetve az apnoe-hypopnoe átlagideje (AHI-átlagideje) [t(22)=5,720, p<0,001]. Az alvás alatti légzésparaméterek közül szignifikánsan javult a legkisebb szaturáció (minimum-SaO₂) [t(22)=-7,911, p<0,001] és az átlagszaturáció (mean SaO₂) [t(22)=-2,353, p=0,028], valamint a deszaturációs index (ODI) [t(22)=15,311, p<0,001].

Diagnosztikus fázis alatti adatfelvétel (1. alkalom) és a két hónapos kontrollvizsgálat alatti adatfelvétel (3. alkalom) összehasonlítása

Alvásstruktúra

A harmadik mérésen, a két hónapos kontrollvizsgálaton poligráfias mérés történt, így csak az alvás alatti légzési eseményeket regisztráltuk.

Alvás alatti légzési események

A két hónapos légszínterápia szignifikáns javulást eredményezett az apnoe-hypopnoe indexben (AHI-index) [t(22)=5,172, p<0,001] és az apnoe-hypopnoe események darabszámában (AHI-esemény) [t(22)=3,853, p=0,001]. További szignifikáns javulást mutatott a legkisebb szaturáció (minimum-SaO₂) [t(22)=-6,698, p<0,001], az átlagszaturáció (mean SaO₂) [t(22)=-3,869, p<0,001] és a deszaturációs index (ODI) [t(22)=10,173, p<0,001].

Titrálás alatti adatfelvétel (2. alkalom) és a két hónapos kontrollvizsgálat alatti adatfelvétel összehasonlítása (3. alkalom)

Alvásstruktúra

A poligráfias mérés következtében csak az alvással alatti légzési eseményeket rögzítettük.

Alvás alatti légzési események

Második alkalommal a titráláson és a harmadik alkalommal, a két hónapos kontrollvizsgálat alatt mért légzési változók közül az apnoe-hypopnoe események száma (AHI-esemény) [t(23)=-1,777, p=0,089] és az átlagidejük (AHI-átlagidő) [t(23)=-1,864, p=0,075] tendenciaszerűen romlottak, de az apnoe-hypopnoe index (AHI-index) értéke nem [t(23)=-1,655, p=0,112]. A legkisebb szaturáció (minimum-SaO₂) [t(23)=0,757, p=0,457], az átlagszaturáció (mean SaO₂) [t(23)=-1,124, p=0,273] és a deszaturációs index (ODI) [t(23)=0,702, p=0,490] értékei nem mutattak szignifikáns változást.

A KOGNITÍV FUNKCIÓK ÉS A SZORONGÁS KAPCSOLATA AZ ALVÁSMUTATÓKKAL ÉS AZ ALUSZÉKONYSÁGGAL

A diagnosztikai fázis (1. alkalom) és az első tesztfelvétel (titrálás) közötti kapcsolatok

Kezelés előtti alvásstruktúra és a kezelés előtti kognitív funkciók kapcsolata

A betűfluencia-teszten a felsorolt szavak száma közepesen erős pozitív korrelációt mutatott a NREM 3. stádiumban megjelenő alvási orsók számával (S3 orsó) [r(13)=0,551, p=0,033]. Szintén mérsékelten erős pozitív korreláció jelent meg a mélyalvással (SWS) [r(13)=0,535, p=0,040] és erős pozitív korrelációban állt a NREM 4. stádium időtartamával (S4 időtartam) [r(13)=0,672, p=0,006]. Emellett a NREM 4. stádium időtartamával a teljes alvásidőhöz képest (S4 TST) [r(13)=0,749, p=0,001], illetve a NREM 4. stádiumban megjelenő δ -hullámok mennyiségével (S4 δ) [r(13)=0,7, p=0,004]. Tehát minél jobban nőtt a NREM 4. stádium időtartama és az itt megjelenő δ -hullámok mennyisége, annál jobban emelkedett a felsorolt szavak száma a betűfluencia-teszten. A szemantikus fluencia feladat erős pozitív korrelációt mutatott a NREM 3. stádiumban megjelenő alvási orsózással (S3 orsó) [r(13)=0,723, p=0,001] és a NREM 4. stádiumban megjelenő alvási orsók számával (S4 orsó) [r(13)=0,674, p=0,006], valamint közepesen erősen pozitívan korrelált a NREM 4. stádium időtartamával a teljes alvásidőhöz képest (S4 TST) [r(13)=0,525, p=0,045]. Az álszóteszt erős negatív

korrelációt mutatott a NREM 2. stádium idejével a teljes alvásidőhöz képest (S2 TST) [r(21)=-0,899, p<0,001], a NREM 2. stádium latenciájával (S2 lat) [r(13)=-0,836, p<0,001], a NREM 2. stádium alvásperiódus idejével (S2 SPT) [r(13)=-0,620, p=0,014] és a NREM 2. stádiumban megjelenő alvási orsók számával (S2 orsó) [r(21)=-0,755, p=0,001]. A NREM 2. stádiumban megjelenő gyors szemmozgás (S2 REM) közepesen erős negatív korrelációt mutatott a fordított számterjedelem teszttel [r(13)=-0,538, p=0,039] és a Corsi-teszttel [r(13)=-0,581, p=0,023] is. Nem szignifikáns, de közepesen erős negatív korreláció jelent meg a betűfluencia-feladaton az összesen visszamondott szavak száma, a NREM 2. stádium latenciája (S2 lat) [r(13)=-0,456, p=0,087], valamint a NREM 2. stádium alvásperiódus-ideje (S2 SPT) [r(13)=-0,463, p=0,082] között. A Rivermead-teszten a történet azonnali felidézése a NREM 2. stádium alvásperiódus idejével (S2 SPT) [r(13)=-0,418, p=0,121], a fordított számterjedelem teszt a NREM 2. stádium latenciájával (S2 lat) [r(13)=-0,413, p=0,126], a szemantikus fluencia feladaton az összesen visszamondott szavak száma pedig a NREM 2. stádiumban megjelenő gyors szemmozgással (S2 REM) mutatott nem szignifikáns, de közepesen erős negatív korrelációt [r(13)=-0,442, p=0,099]. A számterjedelemteszt közepesen erős pozitív korrelációban állt a NREM 3. stádium alatt megjelenő alvási orsók számával (S3 orsó) [r(13)=0,535, p=0,040] és a NREM 4. stádium alvási orsóinak a számával (S4 orsó) [r(13)=0,587, p=0,022]. A fordított számterjedelem teszt már erős pozitív korrelációban állt a NREM 3. stádium alvási orsóival (S3 orsó) [r(13)=0,605, p=0,017] és a NREM 4. stádium alvási orsózással (S4 orsó) [r(13)=0,629, p=0,012]. Akárcsak a hallási mondatterjedelem teszt, mely szintén erős pozitív korrelációt mutatott a NREM 3. stádiumban megjelenő alvási orsókkal (S3 orsó) [r(13)=0,703, p=0,003] és a NREM 4. stádiumban megjelenő alvásiorsó-aktivitással (S4 orsó) [r(13)=0,746, p=0,001]. Ennek alapján az egyre komplexebb feladatok egyre szorosabb összefüggést mutattak a NREM 3. és 4. stádiumokban megjelenő alvási orsókkal.

A kezelés előtti alvásstruktúra és a kezelés előtti szorongási mutatók kapcsolata

A Spielberger-féle Állapot-Vonás Szorongás teszten az állapotszorongás közepesen erős negatív korrelációt mutatott a NREM 4. stádium latenciájával (S4 lat) [r(13)=-0,653, p=0,008]. Nem szignifikáns, de közepesen erős negatív korrelációban állt a NREM 3. stádiumban megjelenő alvási orsókkal (S3 orsó) [r(13)=-0,408, p=0,131], akár-

csak a NREM 4. stádiumban megjelenő alvási orsózással [$r(13)=-0,456$, $p=0,087$] és a REM-fázis latenciájával [$r(13)=-0,500$, $p=0,057$]. A vonásszorongás a NREM 1. stádium lassú szemmozgásával (S1 SEM) [$r(13)=-0,680$, $p=0,005$] állt közepesen erős negatív, a REM-fázisban a lassú szemmozgással (REM SEM) [$r(13)=-0,560$, $p=0,030$] pedig közepesen erős pozitív korrelációban. Emellett nem szignifikáns, de közepesen erős pozitív korrelációban állt a REM-fázis alvásperiódus idejével (REM SPT) [$r(13)=0,414$, $p=0,125$] és közepesen erős negatív korrelációban az alvás alatti ébrenlétek mennyiségével (TWK) [$r(13)=-0,470$, $p=0,077$] és az ébredési indexszel [$r(13)=-0,416$, $p=0,123$].

Diagnosztikus fázis (1. alkalom) és az első tesztfelvétel (titrálás) közötti kapcsolatok

A kezelés előtti légzési események és a kezelés előtti kognitív funkciók kapcsolata

A betűfluencia-feladaton a felsorolt szavak száma erős negatív korrelációt mutatott a teljes alvásidőre vonatkozó légzészavarindexszel (RDI TST) [$r(12)=-0,694$, $p=0,004$] és a NREM-fázis légzészavarindexével (RDI NREM) [$r(13)=-0,678$, $p=0,005$], valamint gyenge negatív korrelációban állt az apnoe-hypopnoe darabszámával (AHI-esemény) [$r(21)=-0,494$, $p=0,017$]. Azaz minél jobban csökkentek a légzési események értékei, annál több szót tudtak felsorolni a betűfluencia-feladaton. A szemantikus fluenciánál az összesen felsorolt szavak száma erős negatív korrelációban állt a teljes alvásidő (RDI TST) [$r(13)=-0,723$, $p=0,002$], a NREM (RDI NREM) [$r(13)=-0,702$, $p=0,004$] és a REM (RDI REM) [$r(13)=-0,643$, $p=0,010$] alvásfázisok légzészavarindexével, illetve gyenge negatív korrelációt mutatott az apnoe-hypopnoe darabszámával (AHI-esemény) [$r(21)=-0,453$, $p=0,030$]. A Rivermead Viselkedéses Emlékezeti teszten a történet azonnali felidézése közepesen erős negatív korrelációban állt a NREM alatti (RDI NREM) [$r(13)=-0,575$, $p=0,025$] és a teljes alvásidő alatti légzészavarindexszel (RDI TST) [$r(13)=-0,556$, $p=0,031$]. A történet késleltetett felidézése szintén közepesen erős negatív korrelációt mutatott a NREM (RDI NREM) [$r(13)=-0,585$, $p=0,022$] és a teljes alvásidő alatti légzészavarindexszel (RDI TST) [$r(13)=-0,595$, $p=0,019$].

A kezelés előtti alvás alatti légzési események és a szorongás kapcsolata

A kezelés előtti légzési események és a szorongás mértéke között nem találtunk közepesen erős vagy erős korrelációt.

A kognitív funkciók és az aluszékonyság kapcsolata
Két hónap alatt csökkent az Epworth Aluszékonysági Skála által mért szubjektív aluszékonyság [$t(19)=4,250$, $p<0,001$], ami a rövid távú verbális epizodikus emlékezeti teljesítménnyel [$r(18)=-0,540$, $p=0,0014$], illetve a végrehajtó funkciókat mérő feladatok változásával korrelált [$r(18)=-0,465$, $p=0,039$].

A kognitív funkciók változása két hónap alatt

Két hónapos légszinterápiát követően szignifikáns javulás jelent meg a Rivermead Viselkedéses Emlékezeti teszten a történet azonnali [$t(23)=-4,309$, $p<0,001$] és késleltetett felidézésén [$t(23)=3,715$, $p=0,001$], valamint a fordított számterjedelem teszten [$t(23)=-3,158$, $p=0,004$] és hallási mondatterjedelem teszten [$t(23)=-2,068$, $p=0,050$]. Tendenciaszintű javulás mutatkozott a Rivermead-teszten a tárgyak azonnali felidézésén [$t(23)=-1,813$, $p=0,083$]. Ezzel ellentétben szignifikáns romlást találtunk a Rivermead-teszten a portré késleltetett felidézésén [$t(23)=3,715$, $p=0,003$], illetve tendenciaszintű romlás jelent meg a végrehajtó funkciókat mérő szemantikus fluenciateszten a perszeverációk számában [$t(23)=-1,813$, $p=0,083$]. A Spielberger-féle Állapot-Vonás Szorongás Teszten szignifikáns javulás jelent meg az állapotszorongás szintjében [$t(21)=2,044$, $p=0,054$] és tendencia szintű javulás mutatkozott a vonásszorongásban is [$t(21)=1,897$, $p=0,072$]. Az első alkalommal, a diagnosztikai fázis és a két hónapos kontrollvizsgálat összehasonlításában, az állapotszorongás változása mérsékelten erős negatív korrelációt mutatott az apnoe-hypopnoe események átlagidejével [$r(19)=-0,573$, $p=0,007$], illetve a vonásszorongás változása is közepesen erős negatív korrelációban állt az apnoe-hypopnoe események átlagidejével [$r(19)=-0,527$, $p=0,014$]. Ez az összefüggés a második alkalommal, a titrálás és a két hónapos kontrollvizsgálat összehasonlításában is megjelent, az állapotszorongás közepesen erős negatív korrelációt mutatott az apnoe-hypopnoe események átlagidejével [$r(20)=-0,576$, $p=0,005$] és a vonásszorongás is közepesen erős negatív korrelációban állt az apnoe-hypopnoe események átlagidejével [$r(20)=-0,467$, $p=0,029$].

NREM 2.-anomáliák

Mivel a kezelés előtt számos negatív korrelációt kaptunk a diagnosztikai fázis alatt regisztrált NREM 2. stádium alvásváltozói és az első alkalommal, a titrálás alkalmával felvett neuropszichológiai teszteredmények között, ezért összehasonlítottuk az eredményeket a második alkalommal, a titrálás alkalmával mért alvásváltozókkal, amikor már készülékekkel aludtak a vizsgálati személyek. A korábbi ne-

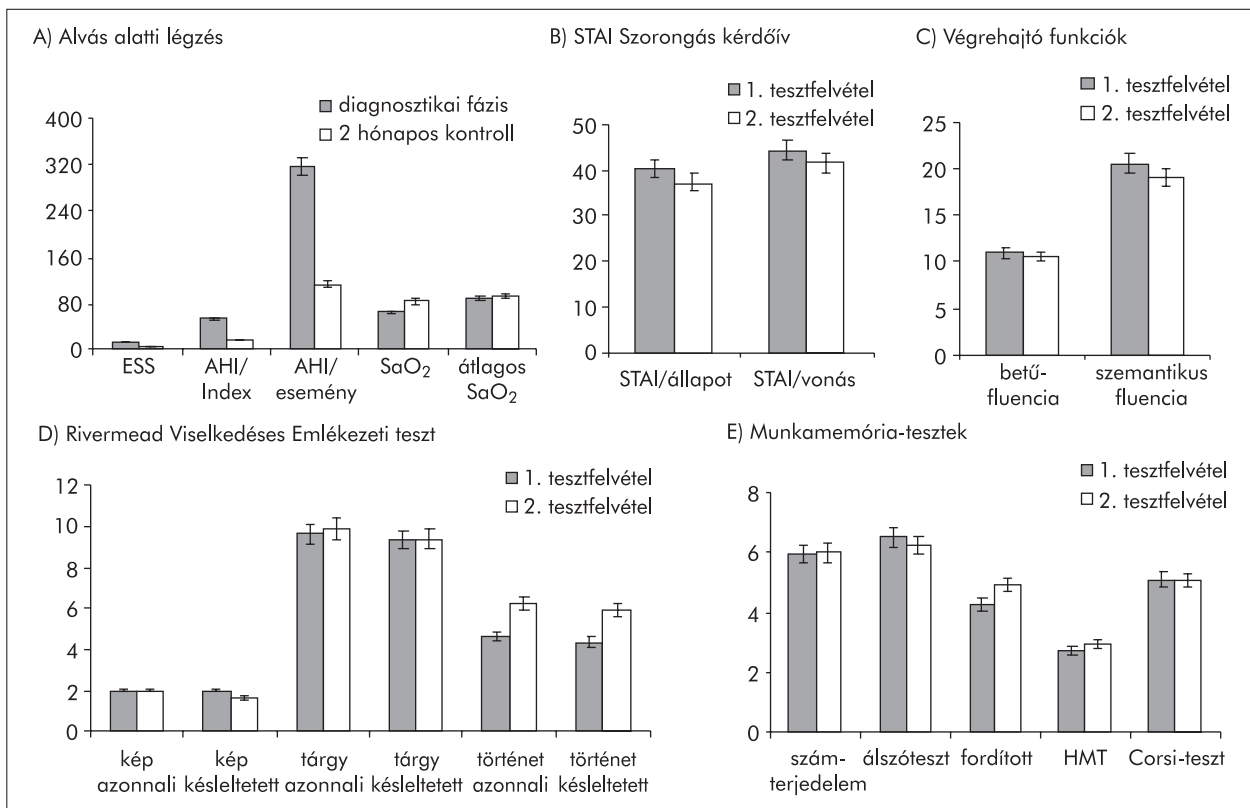
gatív korrelációkkal ellentétben közepesen erős pozitív korrelációt kaptunk a NREM 2. stádiumban megjelenő alvási orsó (S2 orsó) és a fordított számterjedelem között [r(22)=0,412, p=0,045]. A Rivermead-teszten a történet azonnali felidézése a NREM 2. stádiumban megjelenő δ -hullámokkal (S2 δ) [r(22)=0,504, p=0,012], a késleltetett felidézés pedig a NREM 2. alvásperiódus idejével (S2 SPT) [r(22)=0,507, p=0,012] és a teljes alvásidőhöz képest számított alvásidőjével (S2 TST) [r(22)=0,486, p=0,016] állt közepesen erős pozitív korrelációban. Nem szignifikánsan, de közepesen erősen pozitívan korrelált a történet késleltetett felidézése a NREM 2. stádium ágyban töltött idejével (S2 TIB) [r(22)=0,0,467, p=0,021] és az itt megjelenő α -hullámokkal (S2 α) [r(22)=0,502, p=0,056]. A szemantikus fluenciafeladat a NREM 2. stádium alvásidőjével a teljes alvásidő alatt (S2 TST) [r(22)=0,501, p=0,013] és az itt megjelenő alvási orsó számával mutatott közepesen erős negatív korrelációt [r(22)=0,509, p=0,011]. Az itt lévő orsóaktivitással (S2 orsó) a betűfluencia-feladat is közepesen erős pozitív korrelációban állt [r(22)=0,413, p=0,045]. Közepesen erős pozitív korreláció jelent meg a hallási mondatterjedelem teszt és a NREM 2. stádium alvásperiódus-ideje (S2 SPT) [r(22)=0,487, p=0,016], az alvásidője a teljes alvásidő alatt (S2 TST) [r(22)=0,449, p=0,028], az ágyban töltött ideje (S2 TIB) [r(22)=0,474, p=0,019] és az itt megjelenő orsó száma (S2 orsó) [r(22)=0,644, p=0,001] között. Emellett az itt előforduló δ -hullámok (S2) [r(22)=0,403, p=0,051] és a lassú szemmozgás (S SEM) [r(22)=0,436, p=0,033] között. Nem szignifikáns, de közepesen erős korreláció mutatkozott a NREM 2. stádium időtartama (S2 időtartam) és a hallási mondatterjedelem között [r(22)=0,402, p=0,052], mely a NREM 2. stádium idejével a teljes alvásidőhöz képest (S2 TST) is közepesen erős pozitív korrelációban állt [r(22)=0,401, p=0,052].

Megbeszélés

Kutatásunk célja az volt, hogy megvizsgáljuk az alvási apnoe szindróma kezelésére alkalmazott pozitív felső légúti nyomás terápia rövid távú hatását az alvás minőségére, a kognitív funkciókra és a szorongásra. Eredményeink alapján már egy éjszaka után javult az alvás architektúrája. A kezelés előtti állapothoz képest csökkent a felületesebb alvástádiumokban, elsősorban a NREM 1. stádiumban eltöltött idő, ezzel ellentétben megnőtt a REM-alvás és a mélyalvás, azaz a NREM 3. és NREM 4. stádiumok aránya, a teljes NREM-alvás viszont nem változott jelentősen. Csökkent az alvás alatti hypoxiás

epizódok száma, ami javította az alvás alatti légzést és csökkent az ébredések előfordulása, így megnőtt a teljes alvásidő és hatékonyabbá vált az alvás. Két hónapos terápiát követően a kezelés előtti állapothoz képest az alvás alatti légzési eseményekben történő javulás továbbra is fennmaradt, kevesebb hypoxiás epizód jelent meg és nőtt az oxigén-szaturáció, bár a titrálás és a két hónapos kontrollvizsgálat összehasonlításában az apnoe-hypopnoe események átlagideje nem csökkent. Két hónap alatt csökkent az Epworth Aluszékonysági Skála által mért szubjektív aluszékonyság, ami összefüggést mutatott a rövid távú verbális epizodikus emlékezeti teljesítménnyel, illetve a végrehajtó funkciókat mérő feladatok változásával. A kezelést követően javult az állapotszorongás szintje, ami a hypoxiás epizódok csökkenésével függött össze. A kognitív funkcióknál a kezelés előtti és utáni eredményeket összehasonlítva javulást találtunk a komplex munkamemória, valamint a rövid és hosszú távú verbális epizodikus emlékezet működésében, azonban a hosszú távú vizuális emlékezeti teljesítmény a kezelés ellenére romlott. A terápia hatékonyságának vizsgálata mellett külön megnéztük, hogy kezelés előtt az egyes kognitív funkciók és a szorongás milyen kapcsolatban áll az alvási és légzési paraméterekkel. Az eredmények alapján a végrehajtó funkciókat mérő betű- és szemantikus fluenciafeladatok a mélyalvással mutattak szorosabb kapcsolatot, vagyis minél jobban nőtt a mélyalvásban eltöltött idő és az itt megjelenő alacsony frekvenciájú δ -hullámok száma, annál jobban javult a teljesítmény a teszteken. Emellett, az egyre komplexebb, több agyterület együttes működését igénylő feladatok egyre szorosabb összefüggést mutattak a mély alvástádiumokban megjelenő orsóaktivitással. A légzési eseményeknél, a hypoxia a végrehajtó funkciókra, illetve a rövid és hosszú távú verbális epizodikus emlékezetre volt leginkább hatással, minél jobban csökkent a hypoxiás epizódok száma, annál jobban javultak az eredmények a teszteken. Érdekes anomália, hogy a NREM 2. stádium a kezelés megkezdése előtt negatív összefüggést mutatott a verbális és vizuális rövid távú emlékezettel, a komplex munkamemóriával, a végrehajtó funkciókkal, illetve a rövid és hosszú távú verbális epizodikus emlékezettel. Két hónapos kezelést követően a végrehajtó funkciók, a komplex munkamemória, valamint a rövid és hosszú távú verbális emlékezeti teljesítmény a NREM 2. alvástádiummal már pozitív összefüggésben állt. Ennek lehetséges magyarázata, hogy a kezelés hatására a NREM 2. stádium aránya a normál alvásmintázat irányába változott.

Az alvás architektúrája és az alvás alatti légzési események javulása eredményeinkben megegyeznek a *Verma* és munkatársai²⁸, illetve *Morisson* és



1. ábra. A. Szubjektív aluszékonyosság és az alvás alatti légzési események: ESS: Epworth Aluszékonyági Skála; AHI-index: apnoék és hypopnoék százalékos előfordulása; AHI/esemény: apnoék és hypopnoék darabszáma; min SaO₂: legkisebb oxigénszaturáció; átlagos SaO₂: átlagszaturáció. B. Spielberger-féle Állapot-Vonás Szorongás Kérdőív: STAI/állapot: állapot szorongás; STAI/vonás: vonásszorongás. C. Végrehajító funkciók: Betűfluencia; Szemantikus fluencia. D. Rivermead Viselkedéses Emlékezeti Teszt: kép azonnali: kép azonnali felidézése; kép késleltetett: kép késleltetett felidézése; tárgy azonnali: tárgyképek azonnali felidézése; tárgy késleltetett: tárgyképek késleltetett felidézése; történet azonnali: történet azonnali felidézése; történet késleltetett: történet késleltetett felidézése. E. Munkamemória tesztek: számterjedelemteszt; álszóteszt: álszóisméltési teszt; fordított: fordított számterjedelemteszt; HMT: hallási mondatterjedelem teszt; Corsi-teszt: Corsi-kockák teszt. A szóródási mutató az átlagos standard hiba (SEM)

munkatársai³⁶ által kapott eredményekkel, akik szintén csökkenést találtak a légszinterápia hatására a felületes alvásstádiumokban, a légzészavarindexben, valamint növekedést a mélyalvásban és a REM-fázisban. *Heinzer* és munkatársai²⁵ az alvás alatti légzés javulása mellett a lassú hullámú aktivitás nagyarányú növekedését regisztrálták egy napos és kilenc hónapos kezelést követően. Eredményeinkkel ellentétben *McArdle* és *Douglas*⁷⁰ bár javulást találtak az alvás minőségében egy éjszaka után, csökkent a felületes alvás és az ébredések száma, illetve nőtt a mélyalvás, azonban nem találtak javulást a REM-alvásban, aminek oka lehet, hogy mérsékelten súlyos apnoés betegeket néztek, és az ő esetükben több a REM-fázis aránya. *Parrino* és munkatársai²⁶ annak ellenére, hogy csökkenést találtak a NREM 1. stádiumban, az ébredések megjelenésében és a légzészavarindexben, valamint növekedést a mélyalvás és a REM arányában, nem mutattak ki növekedést a teljes alvásidőben. Vizsgálatainktól eltérően ők egy hónapos kezelési intervallu-

mot néztek, ami lehet, hogy még nem elég az alvás-mintázat rendeződéséhez, illetve egy meghatározott alvásórát mértek, ami után felébresztették a vizsgálati személyeket. *Loredó* és munkatársai⁴⁰ egyhetes CPAP-kezelés ellenére sem a teljes alvásidőben, sem az alvás struktúrájában nem találtak javulást placebo-CPAP-csoporttal összehasonlítva, ami magyarázható a kezelési idő rövidségével vagy a nem megfelelő CPAP-nyomással.

Eredményeink alapján a két hónapos légszinterápia hatására javulás jelent meg nemcsak a szubjektív aluszékonyágban, hanem a szorongásban, a kognitív funkciók közül pedig a komplex munkamemória és a rövid, valamint hosszú távú verbális epizodikus emlékezet működésében. A kezelés ellenére azonban a téri-vizuális emlékezeti teljesítmény romlást mutatott. A munkamemória javulásával kapcsolatban megegyező eredményeket kaptunk, mint *Felver-Grant* és munkatársai⁵¹, akik három hónapos kezelést követően mutatták ki ugyanezt, bár eredményeinkkel ellentétben náluk nem jelent meg javulás az epizodi-

kus emlékezeti működésben, ami jelezheti, hogy a munkamemória a legérzékenyebb a légszínterápiás kezelés hatásaira. *Bedard* és munkatársai¹⁸ eredményeinkkel megegyezően hat és 10 hónapos kezelés után mind az azonnali, mind a késleltetett visszahívási kondícióban javulást regisztráltak a verbális emlékezeti feladatokban, illetve a végrehajtó funkciókon kívül minden figyelemre érzékeny teszten, ami a figyelemi funkciók jelentőségét mutatja, javulása teljesítménynövekedést okozhat a többi teszten is. *Borak* és munkatársai⁴⁶ szintén javulást kaptak a verbális emlékezeti működésben, azonban eredményeinkkel ellentétben nem mutattak ki romlást a téri-vizuális emlékezet működésében, éppen ellenkezőleg, javulást találtak, amit okozhatott, hogy vizsgálati személyeket három hónapos kezelés után tesztelték újra. A téri-vizuális memóriában megjelenő romlást eredményeinkkel összhangban *Ferini-Strambi* és munkatársai⁷ is kimutatták 15 napos és négy hónapos CPAP-kezelést követően, ami vizsgálatukban a hypoxiás események előfordulásával függött össze, alátámasztva azt a feltételezést, hogy az oxigénhiányos állapot okozhat olyan strukturális változást a központi idegrendszerben, ami nem vagy csak hosszabb távú kezeléssel fordítható vissza. Az általunk kapott eredményekkel ellentétben *Thomas* és munkatársai²⁷ két hónapos CPAP-kezelés ellenére nem találtak javulást a munkamemóriában, nem állt helyre az aktivitás a dorsolateralis prefrontális területeken a hypoxiás epizódok csökkenésétől függetlenül, ami alapján feltételezhető, hogy a megfelelő alvásmintázat is szerepet játszhat az intakt működésben. *Barnes* és munkatársai⁴² pedig szintén nyolchetes kezelést követően csak a végrehajtó funkciókban és a figyelemben találtak javulást, amit magyarázhat, hogy enyhe apnoés betegeket vizsgáltak vagy nem volt megfelelő a CPAP-nyomás, akárcsak *Engelman* és munkatársai⁷¹ vizsgálatában, akik szintén csak a végrehajtó funkciókban mutattak ki javulást egy hónapos kezelést követően, a figyelemben, az emlékezeti működésben és a vizuomotoros képességet mérő teszteken nem. Lehetséges, hogy ezeknek a funkcióknak a javulásához hosszabb kezelési idő kell vagy befolyásolta az eredményeket, hogy enyhe apnoés betegeket vizsgáltak. *Monasterio* és munkatársai⁴⁴ sem kaptak pozitív irányú javulást három és hat hónapos kezelést követően a verbális memória, a figyelemi és a végrehajtó funkciókban, bár ezeken a teszteken a kezelés megkezdése előtt is normáltartományba esett a vizsgált személyek teljesítménye.

Két hónapos légszínterápia hatására javulást találtunk a szorongás szintjében, ami a hypoxiás események csökkenésével állt kapcsolatban. Ez megegyezik *Jokic* és munkatársai²¹ eredményeivel, akik egy hónapot, illetve *Engelman* és munkatársai⁴³, akik három hónapot követően találtak javulást az érzelmi

státusban, ami szintén a hypoxiával és a NREM 2. stádium csökkenésével állt összefüggésben. Eredményeinkkel ellentétben *Borak* és munkatársai⁴⁶ valamint *Munoz* és munkatársai⁴⁵ sem három, sem 12 hónapos kezelés után nem találtak javulást a depresszió és a szorongás szintjében, amit magyarázhat, hogy súlyos apnoés betegeket néztek vagy nem használtak elég érzékeny teszteket, amelyek a finomabb változásokat is kimutatják. Illetve vizsgálatunk során a szorongás szintjének javulása a hypoxiás epizódok csökkenésével állt kapcsolatban, *Borak* és munkatársai⁴⁶ viszont a fragmentált alvással találtak összefüggést.

Nem tisztázott kérdés, hogy az alvási apnoe szindrómában megjelenő kognitív károsodás a fragmentált alváshoz vagy a hypoxiás epizódokhoz kapcsolódik. Eredményeink alapján mindkettőhöz, a kezelést megelőzően a végrehajtó funkciókra a mély alvás növekedése és a hypoxiás epizódok csökkenése volt hatással, illetve a hypoxia csökkenése összefüggésben állt a rövid távú emlékezeti teljesítmény növekedésével is. Két hónapos kezelést követően a szubjektív aluszékonyságban megjelenő javulás a rövid távú verbális emlékezeti működéssel és a végrehajtó funkciókban történő változással mutatott kapcsolatot. Eredményeink megegyeznek a *Ferini-Strambi* és munkatársai⁷ által kimutatottakkal, akik szintén a végrehajtó funkciók és a hypoxia között találtak összefüggést, habár az ő esetükben a hypoxia a téri-vizuális képességekre is hatással volt, illetve *Bedard* és munkatársai¹⁸ eredményeivel, akik a végrehajtó funkciókban történő romlást szintén a hypoxiás eseményekkel hozták összefüggésbe. *Engelman* és munkatársai⁷¹ a fragmentált alvással mutattak ki kapcsolatot a végrehajtó funkciók működését igénylő teszteken, *Findley* és munkatársai²³ pedig eredményeinkkel összhangban a végrehajtó funkciók mellett a rövid távú verbális és vizuális emlékezeti teljesítmény és a hypoxia között találtak kapcsolatot, akárcsak *Adams* és munkatársai²², akik a verbális emlékezettel mutattak ki összefüggést.

Összefoglalva, eredményeink alapján a légszínterápiás kezelés már rövid távon javulást eredményez az alvás alatti légzésben és az alvásstruktúrában, helyreállítva ezzel restoratív jellegét, ami csökkenti a napközben megjelenő aluszékonyságot. Pozitív változást okoz a pszichés státusban, valamint a kognitív neuropszichológiai funkciókban. Következésképpen az obstruktív alvási apnoe szindróma következtében kialakuló dementia bizonyos – elsősorban frontális területekhez is köthető – funkciókat tekintve reverzibilis.

KÖSZÖNETNYILVÁNÍTÁS

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