# Intact implicit probabilistic sequence learning in obstructive sleep apnea

DEZSO NEMETH[1]*, ESZTER CSÁBI[1]*, KAROLINA JANACSEK[1]*, MÁRIA VÁRSZEGI[3] and ZOLTAN MARI[4]

[1]Institute of Psychology, University of Szeged, Szeged, Hungary, [2]Graduate School of Educational Sciences, University of Szeged, Szeged, Hungary, [3]Somnocenter, Szeged, Hungary and [4]Department of Neurology, Johns Hopkins Hospital, Baltimore, USA

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**Correspondence**
Dezso Nemeth, PhD, Institute of Psychology, University of Szeged, Hungary, Egyetem u. 2, 6722 Szeged, Hungary.
Tel: +36-62-544-692, +36-62-544-509;
fax: +36-62-544-509;
e-mail: nemethd@gmail.com
*These authors contributed equally to this work.

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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 subcortical 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 inform 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.

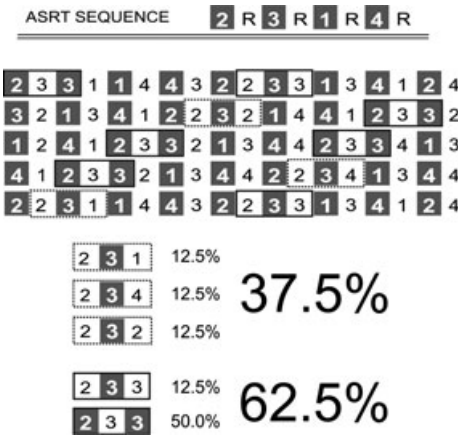


**Figure 1.** In the alternating serial reaction time (ASRT) task, there are more frequent (high-frequency) and less frequent (low frequency) triplets. In other words, if we know what were the last two elements of the sequence (in this case 2–3–?), there is a 67.5% probability of a certain element as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

### 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 × 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 × group interaction: $F_{3,114} = 0.05$, $\eta_p = 0.001$, $P = 0.98$).

The triplet × epoch and triplet × epoch × 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

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 × group interaction: $F_{1,38} = 0.09$, $P = 0.77$; epoch × group interaction: $F_{3,114} = 0.20$, $P = 0.89$; triplet × epoch × 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 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.

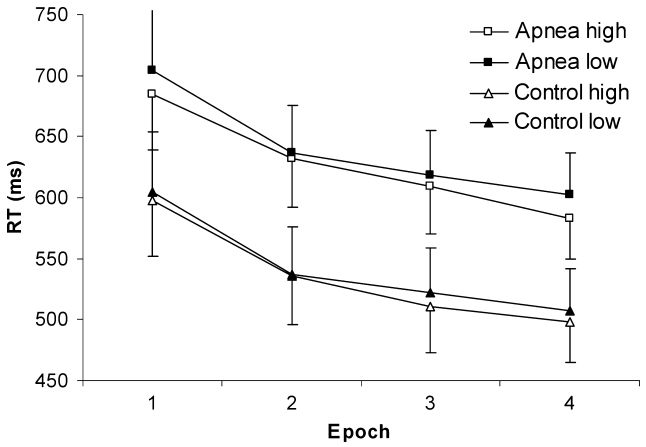


**Figure 2.** Implicit sequence learning in control and sleep apnea group. Both groups showed general skill learning as well as sequence-specific learning. There were no group differences. Error bars indicate standard error of mean.

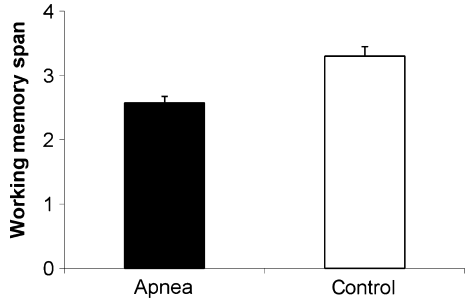


**Figure 3.** Working memory performance in control and sleep apnea group. The working memory span of the sleep apnea group was significantly lower compared to the control group. Error bars indicate standard error of the mean.

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 result 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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