Implicit probabilistic learning: from acquisition to consolidation

Implicit probabilisztikus tanulás: az elsajátítástól a konszolidációig

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The thesis is based on the following articles

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1) Janacsek, K., & Nemeth, D. (2012). Predicting the future: from implicit learning to consolidation. INTERNATIONAL JOURNAL OF PSYCHOPHYSIOLOGY, *83*(2), 213-221.

2) Janacsek, K., Fiser, J., & Nemeth, D. (2012). The best time to acquire new skills: age-related differences in implicit sequence learning across the human lifespan. *DEVELOPMENTAL SCIENCE*, *15*(4), 496-505.

3) Nemeth, D., Janacsek, K., & Fiser, J. (2013). Age-dependent and coordinated shift in performance between implicit and explicit skill learning. *FRONTIERS IN COMPUTATIONAL NEUROSCIENCE*, *7*, 147.

4) Nemeth, D., Janacsek, K., Polner, B., & Kovacs, Z. A. (2013). Boosting human learning by hypnosis. *CEREBRAL CORTEX*, *23*(4), 801-805.

5) Virag, M., Janacsek, K., Horvath, A., Bujdoso, Z., Fabo, D., & Nemeth, D. (2015). Competition between frontal lobe functions and implicit sequence learning: evidence from the long-term effects of alcohol. *EXPERIMENTAL BRAIN RESEARCH*, *233*(7), 2081-2089.

6) Nemeth, D., Hallgato, E., Janacsek, K., Sándor, T., & Londe, Z. (2009). Perceptual and motor factors of implicit skill learning. *NEUROREPORT*, *20*(18), 1654-1658.

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13) Csabi, E., Varszegi-Schulz, M., Janacsek, K., Malecek, N., & Nemeth, D. (2014). The consolidation of implicit sequence memory in obstructive sleep apnea. *PLOS ONE*, *9*(10), e109010.

14) Nemeth, D., & Janacsek, K. (2011). The dynamics of implicit skill consolidation in young and elderly adults. *JOURNAL OF GERONTOLOGY PSYCHOLOGICAL SCIENCE*, *66*(1), 15-22.

15) Hallgato, E., Győri-Dani, D., Pekár, J., Janacsek, K., & Nemeth, D. (2013). The differential consolidation of perceptual and motor learning in skill acquisition.*CORTEX*, *49*(4), 1073-1081.

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1. INTRODUCTION AND AIMS OF THE STUDIES

1.1 Introduction[1]

Prediction is one of the most fundamental functions of the brain. During every moment of our waking life, the brain is trying to anticipate future sensations. In order to recognize time-based patterns and predict subsequent events, storing and recalling of sequences are required (Hawkins, George, & Niemasik, 2009). Without these skills, it would be impossible to carry out evolutionary adaptive behaviors. Most predictions are based on the implicit learning that occurs when information is acquired from an environment of complex stimuli, without conscious access either to what was learned or to the fact that learning occurred (Cleeremans, Destrebecqz, & Boyer, 1998; Reber, 1993). Despite the growing interest in implicit learning in the past decades, there has been relatively little research on the acquisition phase and the offline processing of implicitly learned information (i.e., consolidation). In this thesis, I investigate factors underlying implicit sequence learning and its consolidation. These factors must be taken into consideration before planning and performing brain imaging, psychophysiological, and behavioral studies on sequence learning and its consolidation.

Implicit sequence learning underlies not only motor, but also cognitive and social skills (Kaufman et al., 2010; Lieberman, 2000; Nemeth et al., 2011; Romano Bergstrom, Howard, & Howard, 2012; Ullman, 2004); it is therefore an important aspect of life from infancy to old age. Implicit sequence learning is essential for learning languages, as well as learning to operate appliances, computer applications or musical instruments (J. H. Howard, 2004; Romano Bergstrom et al., 2012). Social skills appear in compound behaviors (including series of perceptions, emotions as well as motor actions) realized in proper sequences and under appropriate circumstances. These skills—for example, dialogues, decision making in social context, communication of emotions, predicting others' behavior based on previous verbal and nonverbal social communication, and adjusting our own behavior based on these predictions—are needed for normal social functioning in various sorts of situations: in the workplace, in the family, in the neighborhood, during recreation, shopping, or in the context of medical and mental care (Heerey & Velani, 2010; Lieberman, 2000; Nemeth & Janacsek, 2011). Furthermore, these skills are crucial for effective participation in educational, training, and

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[1] Based on Janacsek, K., & Nemeth, D. (2012). Predicting the future: from implicit learning to consolidation. *International Journal of Psychophysiology*, *83*(2), 213-221.

rehabilitation programs, for instance in relearning how to walk, reach for objects, and speak after brain injury (D. V. Howard et al., 2004; Nemeth, Janacsek, Balogh, et al., 2010).

Most models and empirical studies of skill learning highlight the role of the basal ganglia and the cerebellum (Dennis & Cabeza, 2011; Doyon, Bellec, et al., 2009; Okihide Hikosaka et al., 1999; O. Hikosaka, Nakamura, Sakai, & Nakahara, 2002; Keele, Ivry, Mayr, Hazeltine, & Heuer, 2003; Kincses et al., 2008; A. Rieckmann, Fischer, & Bäckman, 2010; Sefcsik et al., 2009); in contrast, the role of the hippocampus remains inconclusive (Albouy et al., 2008; Schendan, Searl, Melrose, & Stern, 2003). A major approach to this research is through brain imaging and neuropsychological studies; in addition to these, experiments investigating the effects of pharmacological agents provide an opportunity for the better understanding of the biological background of implicit learning (for review see Uddén, Folia, & Petersson, 2010). For example, a study by Frank et al. (2006) showed that the benzodiazepine midazolam, which inactivates the hippocampus, causes explicit memory deficits in healthy participants, but enhances implicit learning. In contrast, a more recent study found impaired implicit learning after the exogenous administration of the stress hormone cortisol (Römer, Schulz, Richter, Lass-Hennemann, & Schächinger, 2011). The engagement of specific brain structures in these phenomena needs to be clarified.

In experimental settings, implicit learning is defined as the acquisition of co-occurrence/dependencies between stimuli or trials, and is expressed only through performance (Frensch, 1998; D. V. Howard et al., 2004; Anna Rieckmann & Bäckman, 2009). In the past decades, several tasks have been developed to tap into implicit learning. These tasks can be organized into two main groups based on whether the covariation or the temporal sequence of stimuli has predictive information. For example, in artificial grammar learning, participants are exposed to strings of letters. They are not informed that the strings follow a set of rules; yet, it has been found that they can apply these rules at a later stage of practice (Dienes, Broadbent, & Berry, 1991; Reber, 1989). In the weather prediction task, individuals have to decide whether a specific combination of cards predicts rainy or sunny weather. They are unaware that each combination of cards is probabilistically related to a particular weather outcome. During the task, participants learn gradually which of two outcomes will occur, although they have no conscious knowledge of the rule (Gluck, Shohamy, & Myers, 2002; Ferenc Kemény & Lukács, 2009; Kincses, Antal, Nitsche, Bartfai, & Paulus, 2004; Poldrack & Rodriguez, 2004). Similarly, in the contextual cueing task, the global configuration of a display cues the location of a search target (Chun & Jiang, 1998; J. H. Howard, Jr., Howard, Japikse, & Eden, 2006).

In these tasks, the covariation of certain stimuli (e.g., in a letter string/a set of cards) has predictive information, in contrast to sequence learning tasks, where participants have to predict the onset of a stimulus based on the preceding stimuli (Anna Rieckmann & Bäckman, 2009). Evidence suggests that the latter type of task has partly different underlying mechanisms and activates partly different brain structures (Greene, Gross, Elsinger, & Rao, 2007; Luis Jiménez & Vázquez, 2011; Poldrack et al., 2005); therefore, it is important to differentiate between these two types of tasks. In recent years, a growing body of data has emerged regarding the acquisition and consolidation of implicit sequence learning, while covariation learning has received less attention. In my thesis, I focus on the perceptual–motor learning and consolidation of sequences.

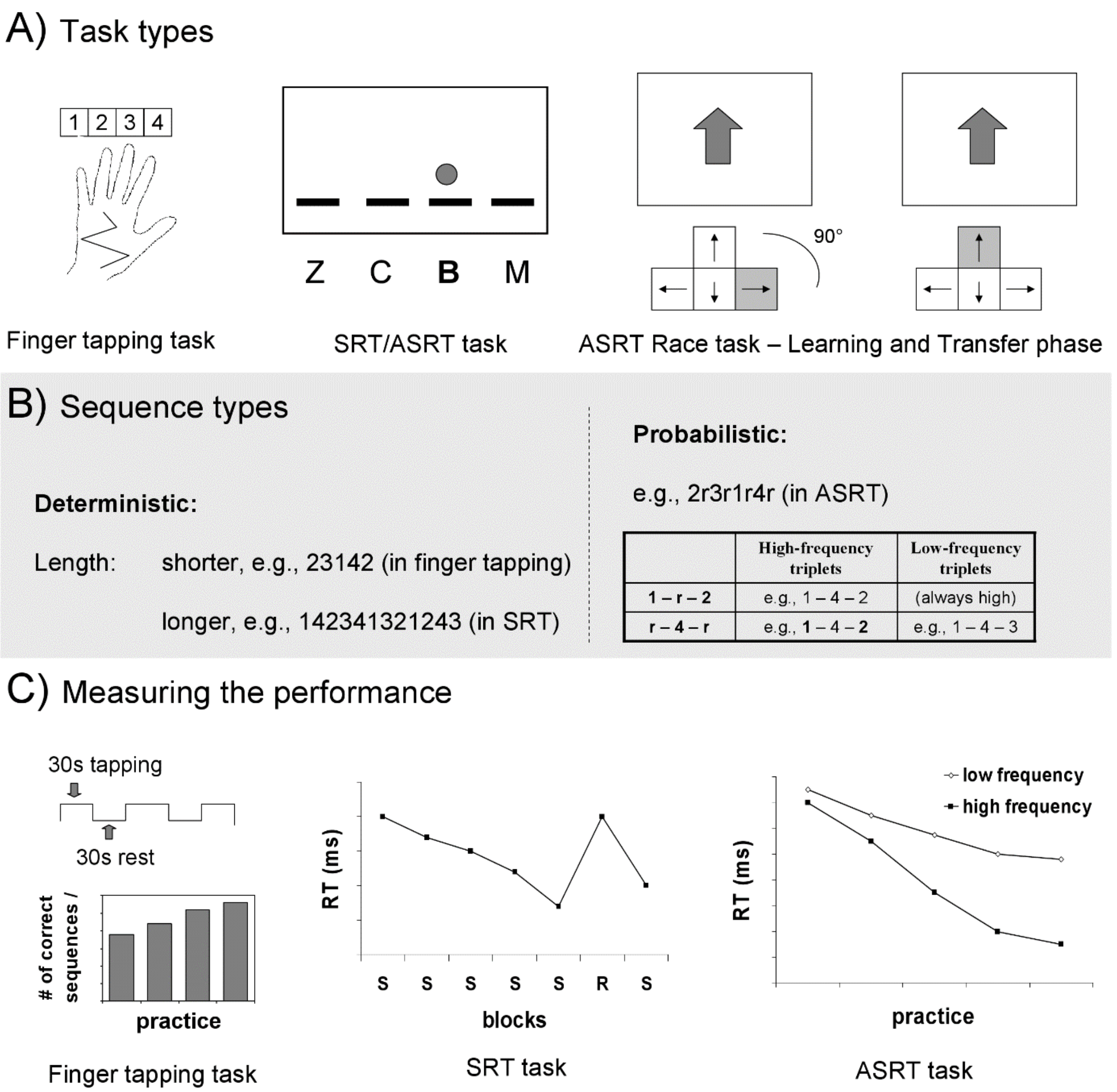
Measures of implicit sequence learning

A widely used sequence learning task is the finger tapping task (Figure 1A). Here, participants are instructed to produce a particular sequence of finger movements either on a response box or by opposing their fingers to their thumb (Doyon et al., 2002; Avi Karni et al., 1995). Performance is measured by the number of correctly produced sequences over a certain time interval (e.g., 30 sec). Similarly to the previously mentioned tasks, participants' performance becomes better with practice. The main problem with this task is that it can be difficult to classify as truly implicit, because participants are aware of the sequence they have to generate. However, it is based on the learning of sequences and the learning is expressed through performance; therefore, I discuss the results based on this task where it is relevant to the question of consolidation.

In the past decade, the serial reaction time (SRT) task (M. J. Nissen & Bullemer, 1987) and its modification, the alternating serial reaction time (ASRT) task (J. H. Howard, Jr. & Howard, 1997; Nemeth, Janacsek, Londe, et al., 2010), have become the most popular implicit sequence learning tasks. In the original version of the SRT task, a stimulus appears at one of four possible locations on the screen, and subjects have to press the button corresponding to that location (Figure 1A). They are unaware that the sequence of subsequent locations (and correspondingly, the sequence of the responses) follows a predetermined order (Hallgato, Győri-Dani, Pekár, Janacsek, & Nemeth, 2013). For example, in classical SRT tasks, the structure of the sequence is deterministic, with the stimuli following a simple repeating pattern as in the series 213412431423, where the numbers refer to distinct events (Figure 1B). Without becoming aware of the sequence, subjects learn the regularity – and as they learn, they produce faster and more accurate responses. When the sequence is changed to a random series of stimuli, subjects become slower and less accurate in responding. In this task, sequence learning is measured by the reaction time difference between sequence and random blocks.

The modified version of SRT is the alternating serial reaction time (ASRT) task (J. H. Howard, Jr. & Howard, 1997; Nemeth, Janacsek, Londe, et al., 2010). Here, repeating events alternate with random ones in an eight-element sequence so that the location of every second stimulus in the stream is determined randomly. If, for instance, the sequence is 3214, where the numbers represent locations on the screen, the sequence of the stimuli will be 3R2R1R4R, with R representing a random element. The sequence is thus better hidden than in the classical SRT task. This structure is referred to as a probabilistic second-order dependency (Remillard, 2008). The structure is second-order in that for pattern trials, event *n-2* predicts event *n*. It is probabilistic in that these pattern trials occur amid randomly determined ones. In addition, participants do not generally become aware of the alternating structure of the sequences, even after extended practice, and sensitive recognition tests indicate that people do not develop explicit knowledge of the event sequences that are more likely to occur (D. V. Howard et al., 2004; J. H. Howard, Jr. & Howard, 1997; Song, Howard, & Howard, 2007b).

Because sequence, and random stimuli alternate in the ASRT task, some sequences of three events (called “triplets”) occur more frequently than others (Figure 1B). In this task we can separate general skill learning from sequence-specific learning, where *general skill learning* refers to increasing speed as the result of practice. In contrast, *sequence-specific learning* refers to the acquisition of sequence-specific knowledge, resulting in relatively faster responses for more predictable high-frequency events compared to less predictable low-frequency events. In the classical SRT task, sequence learning is measured as the RT difference between sequence and random blocks (Figure 1C). However, in this difference score, sequence-specific and general skill learning are mixed, because participants also exhibit general skill improvement on sequential blocks. Thus, the bigger difference between these two types of blocks could be attributed to sequence-specific and general skill learning together, and we cannot determine the extent of these two types of learning. ASRT allows these types of learning to be separated. Another advantage of the ASRT task compared to the classical SRT task is that in the ASRT, it is possible to track sequence-specific learning continuously by comparing responses to the random and sequence elements or more and less predictable events in all blocks. In summary, recent research favors the ASRT task, because 1) it is more implicit, 2) it can separate sequence-specific and general skill learning, and 3) it can continuously track these two types of learning across all blocks.



	High-frequency triplets	Low-frequency triplets
1 – r – 2	e.g., 1 – 4 – 2	(always high)
r – 4 – r	e.g., **1** – 4 – **2**	e.g., 1 – 4 – 3

Figure 1.1. A) Examples of the most commonly used sequence learning paradigms. B) The main distinction in the case of sequence type is whether it is deterministic or probabilistic. C) Typical examples of performance measures in different sequence learning paradigms. In the finger tapping task, performance is measured by the number of correctly produced sequences over a certain time interval (e.g., 30 sec). In the classical SRT task, sequence learning is measured as the RT difference between sequence (S) and random (R) blocks. In the probabilistic sequence learning tasks (e.g., the ASRT task), sequence-specific learning is measured by comparing responses to the random and sequence elements or more and less predictable events in all blocks.

Consolidation of sequence knowledge

Sequence learning does not occur only during practice, in the so-called online periods, but also between practice periods, during the so-called offline periods. The process that occurs during the offline periods is referred to as consolidation, which denotes the stabilization of a memory trace after the initial acquisition; this can result increased resistance to interference or even improvement in performance following an offline period (Krakauer & Shadmehr, 2006; Nemeth, Janacsek, Londe, et al., 2010; Robertson, 2009; Song, 2009).

This thesis will focus on factors that can determine 1) the acquisition phase and 2) the post-encoding stabilization and enhancement phases of consolidation. The consolidation can include the integration of recently acquired information with past experiences (memory association), the anatomical reorganization of memory representations (memory translocation), reconsolidation of memory representations after recall (memory reconsolidation), and even the erasure of memory representations, all of which appear to occur outside of awareness and without additional training. These processes can be time dependent or sleep dependent (Stickgold, Fosse, & Walker, 2002; Walker, Brakefield, Seidman, et al., 2003; Walker & Stickgold, 2004). Hence, it is essential to differentiate between time-dependent and sleep-dependent consolidation. *Time-dependent* consolidation reflects the stabilization or even improvement of the memory trace after an offline period, irrespective of whether sleep occurred in this period or not. Thus, in this type of consolidation, sleep is not an essential component.

In recent decades, special attention has been given to the role of sleep; for instance references are made to *sleep-dependent* consolidation (Walker & Stickgold, 2004) suggesting that performance improves more when the offline period includes sleep than when it does not. Several studies have shown the critical role of sleep in skill learning consolidation (S. Fischer, Hallschmid, Elsner, & Born, 2002; Maquet et al., 2000; Peigneux et al., 2003; Stickgold et al., 2002; Walker, Brakefield, Morgan, Hobson, & Stickgold, 2002). Nonetheless, the results concerning consolidation of sequence knowledge have been mixed, and recent findings indicate that whether or not offline improvements occur at all, and whether they are sleep dependent, varies with factors such as awareness, the length of the offline period, the type of information to be learned, and the age of the participants (Hallgato et al., 2013; Nemeth & Janacsek, 2011; Press, Casement, Pascual-Leone, & Robertson, 2005; Robertson, Pascual-Leone, & Press, 2004; Song et al., 2007b; Spencer, Gouw, & Ivry, 2007).

Although a growing body of research and fertile models advance our understanding of online learning (e.g., N. J. Cohen & Squire, 1980; Hawkins et al., 2009; Henke, 2010; Willingham, 1997), less is known about the offline processes, and there are yet unresolved contradictions between some of the related findings. Therefore, it is critical to determine which factors can potentially influence the consolidation of sequence learning. In the second part of the thesis I will discuss factors that must be taken into account in consolidation research. Considering these factors, it is possible to organize the findings that emerge more appropriately and build more effective models of consolidation.

1.2 Summary of the aims of the studies in the thesis

In the studies presented in this thesis, I explore the entire process of implicit learning from memory formation to consolidation, and investigate how these processes are affected by age, awareness, executive functions, sleep, and various disorders such as Autism, Obstructive Sleep Apnea, and Mild Cognitive Impairment.

The aim of the first part of the thesis is to investigate the factors that can significantly affect implicit probabilistic learning. These factors are summarized in Table 1. More specifically, I investigated how childhood development, aging, atypical development and various neuropsychological conditions such as alcohol dependency and Mild Cognitive Impairment affects the memory formation phase of implicit learning. In addition, I examined how awareness, control, executive functions, and working memory are related to implicit learning, and how perceptual and motor factors are related to each other.

Table 1.1. Factors that can affect implicit learning and the related research questions of the studies presented in the first part of the thesis

Chapter	Factors	Goals and questions
2.1	Childhood development and aging	Which time is the best to acquire new skills? Determine age-related changes across the human lifespan in probabilistic sequence learning
2.2	Age and awareness	What are the differences in the developmental curves of explicit and implicit sequence learning?
2.3	Control processes	How can we boost implicit learning? Determine the competition between control processes and implicit learning
2.4	Executive functions	Can weaker executive functions lead to better implicit learning? Determine the role of executive functions in implicit learning
2.5	Perceptual and motor	How motor and perceptual factors contribute to implicit sequence learning? Determine the perceptual and motor factors of learning
2.6	Secondary task	Can a secondary task disturb implicit sequence learning?
2.7	Working memory	What is the role of working memory in implicit learning?

2.8	Atypical development	How atypical development such as autism affect implicit learning?
2.9	Mild Cognitive Impairment	Can Mild Cognitive Impairment disturb implicit learning? What is the role of the hippocampus in implicit learning?

The aim of the second part of the thesis is to investigate the factors that significantly affects consolidation of implicit probabilistic learning. These factors are summarized in Table 2. More specifically, I investigated how aging, length of the offline period, and sleep affects the consolidation phase of implicit learning. In addition, I examined whether perceptual and motor factors of learning are differentially affected by the offline period following learning.

Table 1.2. Factors that can affect implicit learning and the related research questions of the studies presented in the second part of the thesis

Chapter	**Factors**	**Goals and questions**
3.1	Aging and sleep	What is the role of sleep in the consolidation of implicit learning? Does aging affect sleep-dependent consolidation?
3.2	Aging and length of the offline period	Which length of the offline period is optimal for consolidation: 12h, 24h or 1 week? Is there any interaction between the effects of aging and length of the offline period on consolidation?
3.3	Sleep disorder	Can Sleep disorder disrupt the consolidation of implicit learning?
3.4	Sleep and perceptual-motor factors	Does sleep have a critical role in the consolidation of perceptual and motor factors of implicit learning? Determine the perceptual and motor factors in the consolidation of implicit learning
3.5	Length of the offline period	Is implicitly learned information retained after one year? Is there evidence for resistance to interference after one year?

2. DEVELOPMENTAL AND COGNITIVE FACTORS UNDERLYING IMPLICIT PROBABILISTIC LEARNING

2.1 Age-related changes in implicit probabilistic learning[2]

Abstract

Implicit skill learning underlies obtaining not only motor, but also cognitive and social skills through the life of an individual. Yet, the ontogenetic changes in humans' implicit learning abilities have not yet been characterized, and, thus, their role in acquiring new knowledge efficiently during development is unknown. We investigated such learning across the life span, between 4-85 years of age with an implicit probabilistic sequence learning task, and we found that the difference in implicitly learning high vs. low probability events - measured by raw reaction time (RT) - exhibited a rapid decrement around age of 12. Accuracy and z-transformed data showed partially different developmental curves suggesting a re-evaluation of analysis methods in developmental research. The decrement in raw RT differences supports an extension of the traditional 2-stage lifespan skill acquisition model: in addition to a decline above the age 60 reported in earlier studies, sensitivity to raw probabilities and, therefore, acquiring new skills is significantly more effective until early adolescence than later in life. These results suggest that due to developmental changes in early adolescence, implicit skill learning processes undergo a marked shift in weighting raw probabilities vs. more complex interpretations of events, which, with appropriate timing, prove to be an optimal strategy for human skill learning.

Keywords: skill learning, implicit sequence learning, automaticity, Alternating Serial Reaction Time Task (ASRT), development, aging, critical period

It is widely accepted that children should be introduced to sports, music or languages early in their life if they are to develop a high proficiency, because late learners seldom become true champions or elite musicians or gain command of a second language similar to that of a native speaker. These observations contradict traditional measures of the ability of factual learning of declarative memories, which showed that humans become increasingly better at many learning

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[2] Published in Janacsek, K., Fiser, J., & Nemeth, D. (2012). The best time to acquire new skills: age-related differences in implicit sequence learning across the human lifespan. Developmental science, 15(4), 496-505.

tasks up until their late twenties (F. I. Craik & Bialystok, 2006). However, an important component of developing new abilities is related to implicit unconscious statistical learning processes (O. Hikosaka et al., 2002; Keele et al., 2003) that underlie the acquisition of not only motor but also cognitive and social skills (Doyon, Bellec, et al., 2009; O. Hikosaka et al., 2002; Lieberman, 2000; Poldrack et al., 2005; Ullman, 2001). Thus, to understand complex skill acquisition, the characteristics of both explicit declarative and implicit learning, such as the differences in their efficiency across the lifespan, must be clarified. In contrast to declarative memory (Tulving & Craik, 2000), the ontogenetic changes in humans' implicit learning abilities have not yet been comprehensively characterized, and, thus, their role in acquiring new knowledge efficiently during development is unknown. The main goal of our study was to examine age differences in implicit learning across the human lifespan using the same task for all groups.

The computational underpinnings and the neural substrates of these different kinds of learning mechanisms are also controversial (Henke, 2010). Explicit learning has been linked more closely to medial temporal lobes of the cortex (Dennis & Cabeza, 2011; Squire & Zola, 1996). By contrast, implicit skill learning often requires fine-tuning of the perceptual-motor system based on experience; therefore, most models of implicit skill learning emphasize the role of the basal ganglia and the cerebellum (D. A. Cohen, Pascual-Leone, Press, & Robertson, 2005; Dennis & Cabeza, 2011; Doyon, Bellec, et al., 2009; Okihide Hikosaka et al., 1999; O. Hikosaka et al., 2002), whereas the role of the hippocampus remains inconclusive (Albouy et al., 2008; Schendan et al., 2003). However, these models focused mostly on motor skill-related learning with less emphasis on more complex skills that could involve learning abstract cognitive dependencies implicitly. The second goal of our study was to relate our behavioral results to the various computational models of explicit and implicit learning.

Two main approaches to implicit learning emerged in developmental neuroscience with a different assessment of how learning abilities change with age: 1) the developmental invariance model and 2) the age-related changes model. Studies supporting the developmental invariance model of implicit learning failed to find significant age-related differences in learning (Meulemans, Van der Linden, & Perruchet, 1998; Vinter & Perruchet, 2000). In support of this view, infant studies have shown that adult-like implicit learning mechanisms exist even in very early infancy (Clohessy, Posner, & Rothbart, 2001; Saffran, Aslin, & Newport, 1996). Developmental invariance models explain this age-independence by linking implicit (or procedural) learning to evolutionarily primitive brain regions, such as the basal ganglia and the cerebellum. These regions are characterized as early-maturation regions and are relatively resistant to neurological impairments (Reber, 1993).

By contrast, the age-related changes models posit that considerable developmental differences can be observed in implicit learning. Several of these studies found that older children and young adults showed stronger learning effects compared to very young participants (J. Fletcher, Maybery, & Bennett, 2000; Kirkham, Slemmer, Richardson, & Johnson, 2007; Maybery, Maybery, Taylor, & O'Brien-Malone, 1995; K. M. Thomas et al., 2004). These models accept the fronto-striatal origin of such learning, but they focus on evidence of continued development of these regions that form the basis of the behavioral changes with age (e.g., K. M. Thomas et al., 2004). We compared our empirical results using a new approach to the problem of multiple neural substrates of learning proposed by Daw et al. (2005).

Serial reaction time task and the development of implicit learning

In our study, we used a modified version of the Serial Reaction Time (SRT) Task, which is one of most commonly used methods for measuring implicit skill learning. Serial Reaction Time Task is a four-choice reaction time task containing a hidden repeating sequence that the subject comes to predict and learn implicitly (M. J. Nissen & Bullemer, 1987; Poldrack et al., 2005). In an SRT study, Meulemans et al. (1998) found that 6- and 10-year-old children showed similar degrees of learning as young adults. In contrast, Thomas et al. (2004) found that the learning performance of young adults was better than 7- to 10-year-old children. Studies investigating implicit skill learning at older ages also revealed inconsistent results. For example, several studies have demonstrated that, for simple repeating patterns (in the SRT task), the extent of implicit sequence learning in elderly adults was comparable to young adults (Frensch & Miner, 1994; D. V. Howard & Howard, 1989, 1992). Moreover, in a recent study, Gaillard et al. (2009) found that young (22-year-old), middle-aged (45-year-old), and elderly (71-year-old) participants performed at the same level.

The studies mentioned above used fixed (deterministic) sequences, which can be easily learned, making it less possible to detect age-related differences in learning. Furthermore, they cannot purely determine the acquired sequence-specific knowledge because these tasks (finger-tapping, classical SRT) confound general improvements with sequence-specific learning. Here, we used a modified version of the SRT task, the Alternating Serial Reaction Time (ASRT) task (J. H. Howard, Jr. & Howard, 1997), which enabled us to measure the “pure” sequence-specific learning distinguished from general improvements. In the classical SRT task, the structure of a sequence is deterministic with the stimuli following a simple cyclically repeating pattern (e.g., 213412134121341213412…, where numbers refer to distinct events within the repeating 21341 pattern). By contrast, in the ASRT task (J. H. Howard, Jr. & Howard, 1997; Remillard, 2008), repeating events alternate with random ones. Thus, the location of every second stimulus on the screen was determined randomly. If, for instance, the sequence was 12341234…, where the numbers represent locations on the screen, the sequence of stimuli would be 1R2R3R4R1R2R3R4R… in the ASRT paradigm, with R representing a random element. Therefore, the location of every second stimulus on the screen was determined randomly. Because fixed, sequence-specific and random stimuli were alternating, some sequences of three events (called 'triplets') occurred more frequently than others. For example, in the above illustration 1x2, 2x3, 3x4 and 4x1 would occur often, whereas 1x3 or 4x2 would occur infrequently. Following previous studies, we referred to the former as *high-frequency* triplets and the latter as *low-frequency* triplets (Nemeth, Janacsek, Londe, et al., 2010; Song et al., 2007b). Previous studies have shown that as people practice the ASRT task, they respond more quickly to the high than low frequency triplets, revealing probabilistic, sequence-specific learning (J. H. Howard, Jr. & Howard, 1997; Song et al., 2007b). This learning is statistical in nature because it depends on the frequency of the event sequences. Thus, the RT difference between the high and low frequency triplets in this ASRT task is a measure of human sensitivity to the relative raw probabilities of events observed implicitly in their environment (Perruchet & Pacton, 2006). In addition, the participants are not generally aware of the alternating structure of the sequences, even after extended practice, or when sensitive recognition tests are used to assess explicit knowledge (D. V. Howard et al., 2004; J. H. Howard, Jr. & Howard, 1997; Song et al., 2007b). Thus, the ASRT task is more implicit than the classical deterministic sequence learning tasks.

Using the ASRT task, recent studies have shown that, although elderly adults can also learn the higher-order structure of these complex sequences, they showed age-related deficits (D. V. Howard et al., 2004; J. H. Howard, Jr. & Howard, 1997; Nemeth, Janacsek, Londe, et al., 2010). Both young and elderly adults were able to learn third-order dependencies (1RR2RR3RR1RR2RR3RR…) although the elderly participants performed at a lower level than the younger participants (Bennett, Howard, & Howard, 2007). Whereas several studies investigated implicit learning in children using the ASRT task (Barnes et al., 2008; Barnes, Howard, Howard, Kenealy, & Vaidya, 2010; Nemeth, Janacsek, Balogh, et al., 2010), no child-adult comparison of implicit skill learning performance has yet been reported.

In summary, previous studies have addressed the development and aging in implicit skill learning, but no studies have examined age-related differences from childhood to old age with identical methods. Furthermore, in contrast to general skill improvements, using a probabilistic sequence learning task (ASRT) can help us to reveal the age-related differences of the underlying mechanisms of complex skill learning by measuring explicitly the sensitivity to raw probabilities of high and low frequency events. Therefore, in this study, we compared the implicit probabilistic sequence learning across the age range of 4-85 years.

Method

Participants

There were 421 participants in the experiment between the ages of 4 and 85 that were clustered into nine age groups between 4-6, 7-8, 9-10, 11-12, 14-17, 18-29, 30-44, 45-59 and 60-85 years of age (Table 1.1). None of them suffered from any developmental, psychiatric or neurological disorders. All subjects gave signed informed consent (parental consent was obtained for children), and they received no financial compensation for participation. All experimental procedures were approved by the Ethics Committee of the University of Szeged.

Group	Age	Sex	Education	Mean RT (ms)	Mean Accuracy (%)
4-6-year-old (n=30)	5.31 (0.98)	17 M / 13 F	-	960.06 (214.67)	90.09 (6.34)
7-8-year-old (n=55)	7.09 (0.56)	31 M / 24 F	1.18 (0.39)	773.24 (159.29)	90.66 (7.03)
9-10-year-old (n=35)	9.89 (0.58)	14 M / 21 F	3.2 (0.96)	602.84 (121.03)	93.44 (4.21)
11-12-year-old (n=29)	11.5 (0.5)	21 M / 8 F	4.66 (0.67)	544.15 (95.00)	92.52 (4.23)
14-17-year-old (n=62)	14.89 (1.06)	46 M / 15 F	8.23 (1.02)	452.52 (67.06)	95.44 (2.92)
18-29-year-old (n=63)	23.09 (3.67)	40 M / 23 F	15.45 (2.6)	401.79 (50.85)	95.47 (2.45)
30-44-year-old (n=59)	35 (4.24)	24 M/ 35 F	16.64 (3.1)	419.85 (58.68)	95.85 (2.98)
45-59-year-old (n=36)	50.8 (5.07)	12 M / 24 F	14.18 (3.58)	526.7 (112.99)	97.4 (3.45)
60-85-year-old (n=52)	69.85 (6.16)	16 M / 36 F	13.39 (3.04)	634.37 (126.54)	96.92 (2.38)

Table 1 Demographic data and mean RT and accuracy in the different groups. In all columns, numbers in parentheses show standard deviation.

Implicit probabilistic sequence learning task

We used the ASRT task (J. H. Howard, Jr. & Howard, 1997; Nemeth, Janacsek, Londe, et al., 2010) where a stimulus (a dog's head) appeared in one of the four empty circles arranged in a line on a computer screen. The participants were instructed to respond to different stimulus events by pressing the corresponding response keys (Z, C, B or M) as fast and accurately as possible. The ASRT task consisted of 20 blocks with 85 key presses in each block. The first five responses of each stimulus block served for practice only, and then the eight-element alternating sequence (e.g., 1R2R3R4R) was repeated ten times within a block. Stimuli were presented 120 ms after the response to the previous stimulus. Between blocks, the participants received feedback on the screen about their overall reaction time (RT) and accuracy. The computer program generated a different repeating ASRT sequence of the 4 locations for each participant using a permutation rule such that each of the six unique permutations of the 4 repeating events occurred with equal probability.

To determine the amount of explicit knowledge the subjects acquired about the task, a short questionnaire was administered after the experimental session (Song et al., 2007b). 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-point scale where 1 denoted "Nothing noticed" and 5 denoted "Total awareness". None of the participants, young or old, reported noticing the hidden repeating sequence.

Statistical properties of the ASRT task

As mentioned above, the ASRT allows a comparison between responses to high- and low-probability events. For example, if the eight-element sequence is 1R2R3R4R, 1x2, 2x3, 3x4, and 4x1 would occur often (high frequency triplets) because two consecutive stimuli of the repeating sequence (e.g., 132 consisting 1R2) as well as two consecutive random elements by chance (e.g., the same 132 consisting R3R) could form these triplets. By contrast, 1x3 or 4x2 would occur less frequently (low frequency triplets) because they could never be obtained consisting two consecutive sequence elements. Of the 64 possible triplets, sixteen triplets were high frequency triplets, occurring 62.5% of the time, whereas the remaining 48 triplets were low frequency triplets, occurring 37.5% of the time. Thus, each low frequency triplet occurred in approximately 0.8% of the total number of trials, whereas each high frequency triplet occurred about 5 times more often, in approximately 4% of the trials. For each keypress response, we defined whether it was in response to a high- or a low frequency element, depending on whether the element was more or less predictable based on the previous two items in the sequence.

Following the method of previous studies (D. V. Howard et al., 2004; Song et al., 2007b), two kinds of low frequency triplets were excluded from our analyses: repetitions (e.g., 222, 333) and trills (e.g., 212, 343). Repetitions and trills were low frequency for all participants, and in previous studies, the participants often showed pre-existing response tendencies towards them (D. V. Howard et al., 2004; Soetens, Melis, & Notebaert, 2004). The elimination of these special triplets from the analyses ensured that the high versus low frequency differences found in the study were not confounded by pre-existing response tendencies. After this adjustment, previous studies have found that, following the practice, participants responded more quickly to the high than to the low frequency triplets, revealing a sequence learning effect (D. V. Howard et al., 2004; J. H. Howard, Jr. & Howard, 1997; Nemeth, Janacsek, Londe, et al., 2010; Song et al., 2007b).

Statistical analysis

We calculated the mean accuracy of all trials and the median reaction time (RT) of correct responses separately for high and low frequency triplets. The accuracy and RT measures were analyzed by mixed-model ANOVA with TRIPLET TYPE (high vs. low frequency) as the within-subject factor, and AGE (9 groups) as the 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 analysis was conducted by Fisher's LSD pairwise comparisons.

Results

Overall RT's significantly differed among the age groups (main effect of AGE: $F(8,412)=107.11$, $p<0.001$, $\eta_p^2=0.675$; Table 1). The RT decreased significantly between each group from 4-6 to 18-29 years of age (all p's<0.04), they were similar between the age groups of 18-29 and 30-44 ($p>0.38$) and significantly increased after 44 years of age (p's<0.001) (Figure 2.1.1a). The accuracy monotonically increased over the years (main effect of AGE: $F(8,412)=16.94$, $p<0.001$, $\eta_p^2=0.25$) (Figure 2.1.1b).

The comparison of RT to high vs. low probability triplets showed a surprising pattern of implicit sequence learning across the age groups. Even though there was a significant learning at all ages because the RT's were faster for high frequency than to low frequency triplets (main effect of TRIPLET TYPE: $F(1,412)=333.7$, $p<0.001$, $\eta_p^2=0.45$, all p's <0.03) (Figure 2.1.1c), the magnitude of this difference was not uniform. Although the age groups differed significantly from each other in sequence learning (TRIPLET TYPE x AGE interaction: $F(8,412)=6.79$, $p<0.001$, $\eta_p^2=0.12$), the post-hoc test revealed that learning was significantly higher in the 4- to 12-year-old groups than in any other group in the 14-85 range (p's<0.02). There was no difference in learning between the 14-59 years of age (p's>0.37), whereas the magnitude of learning decreased significantly in the 60-85-year-old group (p's<0.02). Thus, learning high probability events was uniformly effective until the age of 12 where it reduced significantly and remained at a lower level of sensitivity until the age of 60 (Figure 2.1.1c).

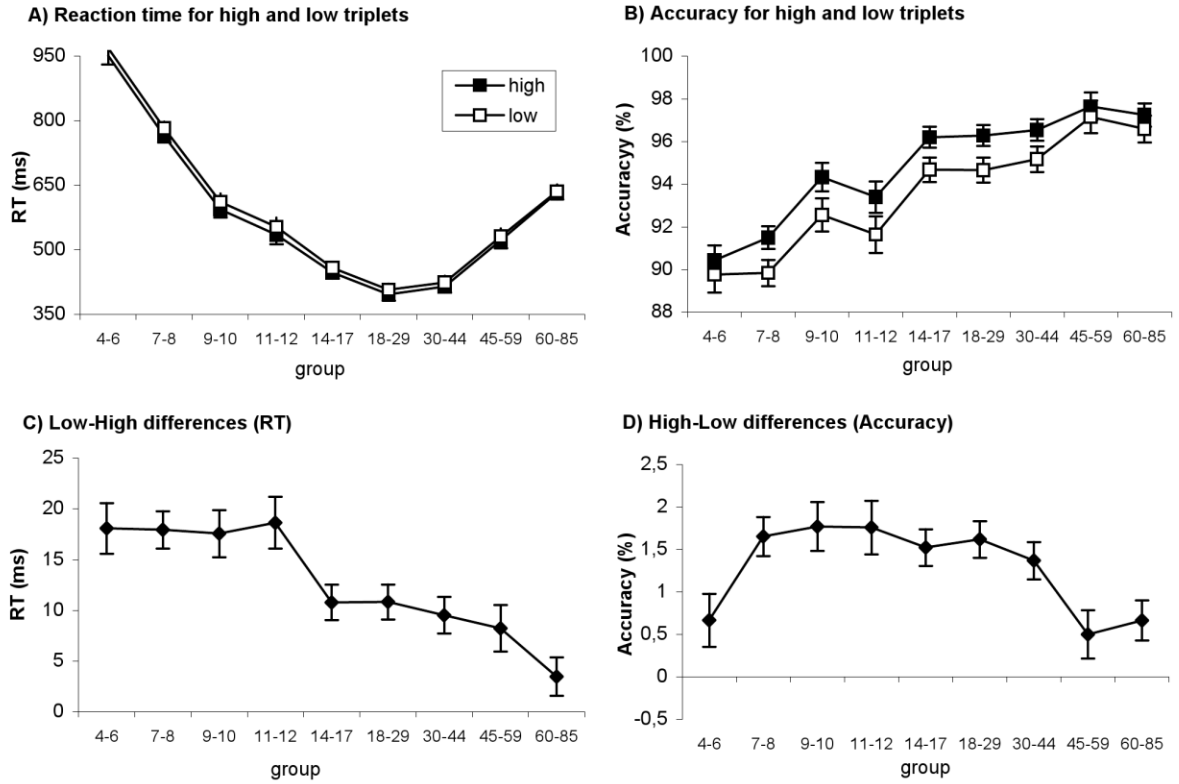

Figure 2.1.1. Sequence learning in all groups. Reaction time (A) and accuracy (B) for high and low frequency triplets are plotted. Learning measures of RT (C) and accuracy (D) represents the RT/ACC difference between low- and high-frequency triplets. Error bars indicate SEM.

However, it is a long-standing issue in developmental and aging studies how to compare groups with different baseline speeds. A customary approach to this problem is to analyze the data using z-transformation. Therefore, we calculated the z-scores within each subject (thus, each participant's own mean and SD was used to transform that participant's data (see, for example, Mattis, 1988) and conducted an ANOVA based on these z-scores (Figure 2.1.2). ANOVA revealed significant sequence-specific learning (main effect of TRIPLET TYPE: F(1,412)=320.12, p<0.001, η_p^2=0.44), but the extent of learning differed across groups (TRIPLET TYPE x AGE interaction: F(8,412)=8.91, p<0.001, η_p^2=0.15). We found that the participants from 9 years of age showed similar extent of sequence learning as the adult groups to 44 years of age (all p’s>0.25), but the learning in 4-8 years of age was smaller compared to these adult groups (all p’s<0.014). At older ages, there was a decline in the sequence learning, with both the 45-59 and 60-85-year-old group differing significantly from the groups between the 11-44 years of age (all p’s<0.025).

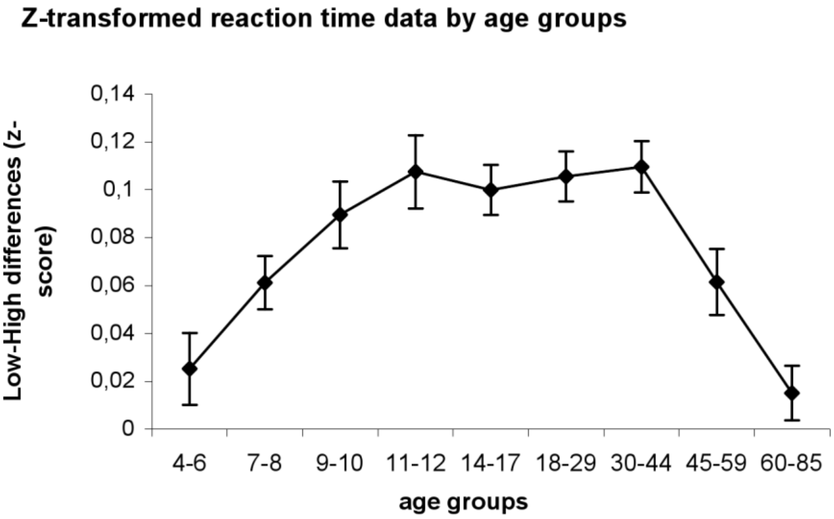

Figure 2.1.2. Sequence learning measured the z-transformed RT data in all groups.

The analysis of the response accuracy further enhanced the picture emerging from the results with RTs. We found a significantly greater accuracy for high- than low-frequency triplets (main effect of TRIPLET TYPE: F(1,412)=217.14, p<0.001, η_p^2=0.345). Although all age groups older than 6 showed significant sequence learning (all p's<0.011), the age groups differed significantly in the strength of the sequence learning (TRIPLET TYPE x AGE interaction: F(8,412)=3.73, p<0.001, η_p^2=0.07). Whereas groups between 7 and 44 years of age showed similar degrees of learning, this was significantly higher than the youngest (4-6) and the two oldest (45-59 and 60-85) groups (p's<0.03) (Figure 2.1.1d).

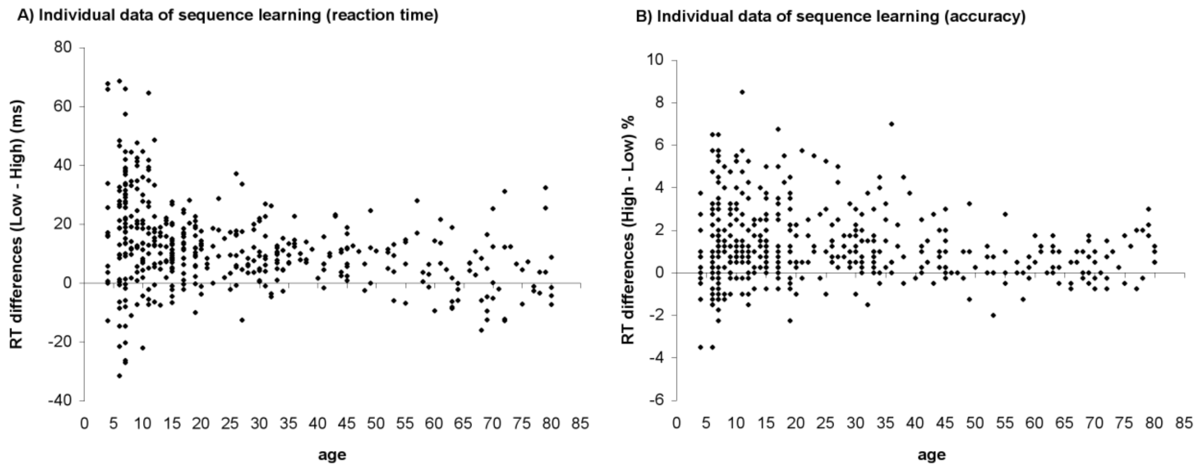

Figure 2.1.3. Individual data for sequence learning measured by raw RT (A),accuracy (B), and z-scores (C) in all ages.

Figure 2.1.3 shows the individual data for sequence learning measured by raw RT, accuracy and z-transformed RT data. The pattern of this data is consistent with the ANOVA results: 1) children between 4-12 years of age showed greater sequence learning as measured by raw RT, whereas 2) in sequence-specific learning as measured by accuracy and z-transformed RTs adults exhibited the highest performance.

Discussion

The goal of the present study was to investigate the differences in implicit skill learning across the human life span. This work extends previous studies (Bennett et al., 2007; Gaillard et al., 2009; J. H. Howard, Jr. & Howard, 1997; Meulemans et al., 1998; K. M. Thomas et al., 2004) in two ways: 1) it examined a wide range of ages between 4-85 years, and 2) it used a probabilistic task, which enabled us to measure the "pure" sequence-specific learning defined by the sensitivity to raw probabilities of high and low frequency events. We found that the 4- to 12-year-old age groups showed the strongest learning effect measured by the raw RT difference scores. Around the age of 12, we found a striking transition to less pronounced sequence-specific learning, as measured by smaller differences between the responses to high and low frequency triplets. Confirming earlier results (D. V. Howard et al., 2004; J. H. Howard, Jr. & Howard, 1997; Nemeth, Janacsek, Londe, et al., 2010), we found that this learning capacity was significantly reduced in the oldest age group. Thus, in contrast to the developmental invariance (Reber, 1993) and the age-related changes approaches (Meulemans et al., 1998; Vinter & Perruchet, 2000), our results demonstrate a gradual decline in learning across the lifespan.

Sequence learning scores based on the accuracy and raw reaction time showed different curves: the former one is a bell-shaped curve, whereas the latter is a gradually declining curve (Figure 2.1.1c-d). Hence, these two types of learning scores can reflect different underlying mechanisms and brain systems. The accuracy learning score may be more related to attention, mainly voluntary attention, whereas the RT learning score may be related to involuntary attention and intuitive processes (Burgess, Gilbert, & Dumontheil, 2007; Prinzmetal, McCool, & Park, 2005). The relatively weaker accuracy learning effects in children and older groups may be due to the underdeveloped/deteriorating attentional brain circuits connected to the frontal lobe.

Our study raised a methodological issue which affects the developmental studies in general. It is a long-standing issue in the literature how to compare groups with different baseline speeds. It could be argued that the youngest groups in our study have larger raw RT learning scores (more difference between high and low frequency triplets) because they have more room to do so, given their longer RTs. However this argument does not seem to hold in our study, because the oldest group showed equally long RTs as 9-10 year-olds, yet they had a four-fold reduced learning score (Figure 2.1.1). Along a similar line of argument, the accuracy measures of the youngest group (4-6 year-olds) and the oldest groups (45-85 year-olds) showed a marked difference (~8%) in general accuracy, giving more room for the young group to produce larger differences between high and low frequency triplets, yet the actual sequence-learning (i.e. high-low differences in accuracy) showed no difference. In contrast, the two smallest age groups had almost identical general accuracy yet there was a more than two-fold increase in sequence learning in the second youngest group (7-8 year-olds). Thus, our data suggests no linear relationship between the general magnitude of reaction time/accuracy and the learning measures.

A second customary approach to the problem of comparing groups with different baseline speeds is to analyze the data using z-transformation. Z-scores of our results show a different picture than raw the RT data analysis: the learning performances from 9 to 44 years of age are similar with weaker performance in the younger and older age groups. The z-transformation is often used to control general processing speed across different age groups in developmental studies. However, the main function of z-transformation is not to control the processing speed, but to normalize the distribution of responses. Thus, z-transformation has mathematical assumptions about the form of distributions and is therefore not theory independent (Yap, Balota, Sibley, & Ratcliff, 2012). Z scoring fully adjusts for processing speed only if all participants have the same type of distributions. Therefore using z-scores in developmental studies might be misleading. Furthermore, it is unclear how general processing speed and variability contributes to learning and performance in different ages. In recent years, several studies analyzed the variability and noise across a wide age-range (Der & Deary, 2006; Hultsch, MacDonald, Hunter, Levy-Bencheton, & Strauss, 2000; Rabbitt, Osman, Moore, & Stollery, 2001). For example, Rabbitt et al. (2001) found that people's fastest RT's were relatively unaffected by age, but the number of unnecessarily slow responses was higher in older ages, and, thus, the increase in the mean RT was a result of increasing variability, which was an important component of cognitive aging. Moreover, several studies outline that the noise and the performance variability enables adaptive plasticity of motor skills (Slifkin & Newell, 1998, 1999; Turner & Brainard, 2007) and high variability can support effective learning and performance (Sanger, 2010). Thus, based on previous studies and on our analyses, we suggest that both the processing speed (mean reaction time) and variability are inherent aspects of development and aging. We think that the z-transformation eliminates these inherent aspects of learning, making the transformed results difficult to understand and explain.

Based on the reasoning above, we propose that, the raw RT difference between the high and low frequency triplets in the ASRT task is a measure of human sensitivity to the relative raw probabilities of events observed implicitly in their environment. Thus, our results show a marked decrease in this sensitivity around the age of 12, which is in contrast to the traditional view of a steady improvement of cognitive learning abilities until late in adulthood (F. I. Craik & Bialystok, 2006). However, this discrepancy might be explained based on a shift in the structural development of implicit learning. Although the raw probabilities of the sensory environment are important for learning and both infants (Aslin, Saffran, & Newport, 1998; Fiser & Aslin, 2002; Saffran et al., 1996; Saffran, Johnson, Aslin, & Newport, 1999) and adults (Fiser & Aslin, 2001; Hunt & Aslin, 2001) are highly sensitive to them, there is an ongoing debate on how using these simple probabilities can lead to highly complex knowledge of the world, such as sensory invariances and development of a language (Gomez & Gerken, 1999; Marcus, Vijayan, Rao, & Vishton, 1999). Recent studies proposed that using an internally stored structured model of the world that emerges based on past experience together with probabilistic learning could help to address this issue and also provide evidence that humans might implement such a strategy during implicit learning (Bird, Lambon Ralph, Seidenberg, McClelland, & Patterson, 2003; Orban, Fiser, Aslin, & Lengyel, 2008). In this framework, as the internal model develops with experiences becoming more influential, internal interpretations of events become more elaborate and less directly related to their raw probabilities. A recent study argued that from a normative standpoint, existence of multiple learning mechanisms in the brain (cf. model-free vs. model-based learning) with an uncertainty–based arbitration between them would be computationally optimal (Daw et al., 2005). Anchoring this hypothesis biologically, the presumed mechanisms related to these two types of learning were suggested to be related to the prefrontal areas and temporal lobe of the cortex, respectively (Daw et al., 2005). Support for the separated and complementary nature of the prefrontal- and medial temporal lobe (MTL)-dependent learning based on internal models vs. basal ganglia-dependent model-free learning comes from various studies investigating learning under specific conditions. These studies showed that obstructing the PFC and/or MTL by a demanding secondary task (Foerde, Knowlton, & Poldrack, 2006) do not adversely affect implicit learning. Other studies found that inserting a task between the learning sessions (R. M. Brown & Robertson, 2007a, 2007b), performing a working memory and an implicit learning task simultaneously (Matilla-Duenas, Corral-Juan, Volpini, & Sanchez, 2012), or a neuropharmacological blockage (M. J. Frank et al., 2006) even had a positive effect on performance in implicit learning task. Importantly, it is known that the cortical areas connected to the internal models related to model-based learning become truly functional late in the development, around age of 12 (Blakemore & Choudhury, 2006; Giedd et al., 1999), which is about the age when we found the sudden decrement in sensitivity to the relative raw probabilities. We propose, that this enhanced functionality signals the shift when the system adapts efficiently to more complex aspects of the world by relying more on internal model-based interpretations, while somewhat neglecting the raw probabilities of the sensory input (Figure 2.1.4a-b), and therefore, decreasing the ability to develop and stabilize fundamentally new basic competences. Thus the seemingly paradoxical result of gradually becoming less sensitive to basic statistics, if timed appropriately, could be the optimal strategy for human implicit learning in general.

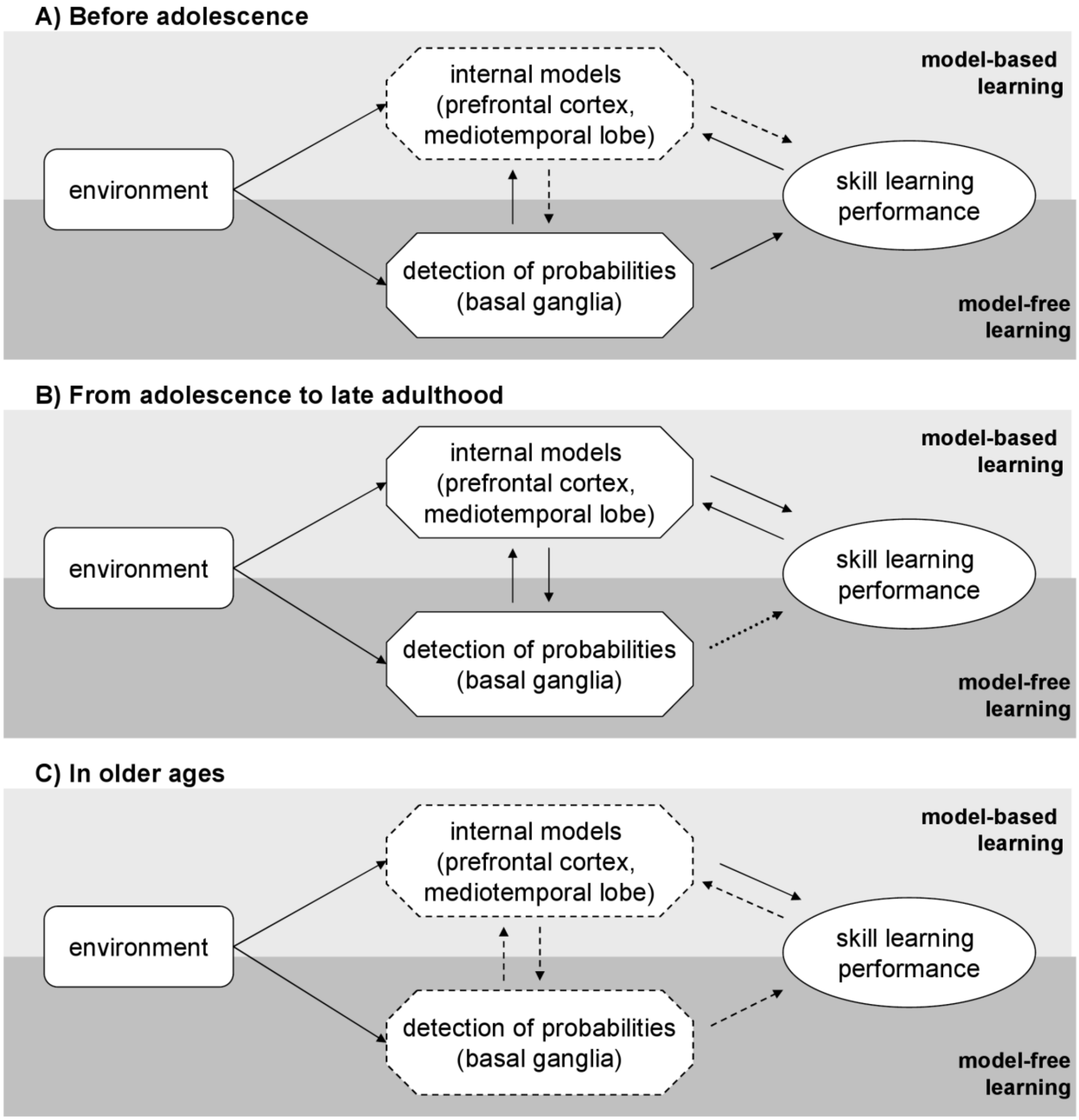

Figure 2.1.4. Competition between model-based and model-free neurocognitive subsystems of skill learning across lifespan. (A) Before adolescence, underdeveloped internal models (dashed boundary) have little influence on interpretations of detected raw statistical probabilities of events in the environment (dashed arrows). Skill learning performance is determined by raw probabilities. (B) From adolescence to late adulthood, well-developed internal models (solid boundary) strongly modulate the interpretations of observed statistics of the input. This helps extracting complex relations but relatively impairs measuring and utilizing raw probabilities in skill learning (dotted arrow). (C) In older ages, skill learning performance decreases. This decline could be caused by the combination of reduced sensitivity to raw statistical probabilities (dashed boundary), increasingly rigid internal models (dashed boundary) and/or weaker connection between these systems (dashed arrows).

Our results did not reveal any differences between the young adults and middle-age groups. Salthouse's (1996) "simultaneity mechanism" theory of cognitive aging predicts the age-related deficits in probabilistic sequence learning (T. Curran, 1997; J. H. Howard, Jr. & Howard, 1997). Feeney, Howard & Howard (2002) found age-related deficits in pattern sensitivity in "older" (mean age: 49.4) compared with "younger" (mean age: 41.4) middle-aged groups. These different results could be related to that Feeney used a smaller sample size, a longer version of the ASRT and different method of analysis.

What are the underlying mechanisms of the decreased performance of the elderly group? In a recent fMRI study, Dennis and Cabeza (2011) showed that older adults recruited the MTL for implicit learning, and this activation was significantly greater, while striatal activity decreased in older people compared with young adults during implicit learning. In a recent study, Rieckmann, Fisher & Backman (2010) found similar results: in young adults during the learning session, the activation of the striatum increased, but the that of MTL decreased. By contrast, in older adults, sequence learning positively related to activation increases in both the striatum and MTL. Using multimodal imaging measures, Giorgo et al. (2010) found extensive reductions in the gray matter volume in aging, but reductions were detected earlier in the frontal cortex. Furthermore, a recent diffusion tensor imaging aging study by Bennett et al. (2011) found that the caudate–dorsolateral prefrontal cortex (DLPFC) and hippocampus-DLPFC tract integrity were related to ASRT sequence learning. The caudate-DLPFC tract integrity decreased in the older ages, mediating age-related differences in sequence learning. Within the computational framework proposed by Daw and collegues (2005), these findings can be interpreted as a deterioration in three mechanisms that contribute to the age-related decline in skill learning: 1) reduced detection of probabilities, 2) rigidity of internal models and/or 3) more restricted connections between internal models and probability detection (Figure 2.1.4c). Thus, not only the model-free, but also the model-based learning, might be limited in older ages. Future studies are needed to systematically examine the underlying neural mechanisms of age-related differences in skill learning.

In summary, based on our raw RT results we suggest that acquiring fundamentally new skills that cannot be derived from skills already possessed is the most effective before adolescence, and it might be largely based on the fronto-striatal circuitry, such as the basal ganglia and cerebellum, in agreement with earlier skill learning models (Doyon, Bellec, et al., 2009; Okihide Hikosaka et al., 1999; O. Hikosaka et al., 2002) and computational learning models (Daw et al., 2005). Our findings are in good agreement with everyday life experience showing that an early (~ before 12 years) start of learning some sports, music instruments, second language, etc. often leads to higher level of competence. These results may have implications for the development of learning and memory, facilitating new skill training and pedagogic methods (e.g., for teaching languages) and may also contribute to the understanding of neurodevelopmental and age-related disorders (e.g., autism, SLI, dyslexia and dementia) and lead to relevant treatment options.

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2.2 Age-related changes in explicit and implicit probabilistic learning[3]

Abstract

It has been reported recently that while general sequence learning across ages conforms to the typical inverted-U shape pattern, with best performance in early adulthood, surprisingly, the basic ability of picking up in an implicit manner triplets that occur with high vs. low probability in the sequence is best before 12 years of age and it significantly weakens afterwards. Based on these findings, it has been hypothesized that the cognitively controlled processes coming online at around 12 are useful for more targeted explicit learning at the cost of becoming relatively less sensitive to raw probabilities of events. To test this hypothesis, we collected data in a sequence learning task using probabilistic sequences in five age groups from 11 to 39 years of age (N=288), replicating the original implicit learning paradigm in an explicit task setting where subjects were guided to find repeating sequences. We found that in contrast to the implicit results, performance with the high- vs. low-probability triplets was at the same level in all age groups when subjects sought patterns in the sequence explicitly. Importantly, measurements of explicit knowledge about the identity of the sequences revealed a significant increase in ability to explicitly access the true sequences exactly around the age where the earlier study found the significant drop in ability to learn implicitly raw probabilities. These findings support the conjecture that the gradually increasing involvement of more complex internal models optimizes our skill learning abilities by compensating for the performance loss due to down-weighting the raw probabilities of the sensory input, while expanding our ability to acquire more sophisticated skills.

Keywords: probabilistic sequence learning, associative learning, development, model-based vs. model free learning

In order to fully understand the mechanism of complex skill acquisition, the defining characteristics of both explicit and implicit learning, such as their efficiency across life span, and their interaction must be clarified. Sequence learning is a prominent component of skill learning, which is involved in obtaining not only motor, but also cognitive and social skills. It is ideally suited to investigate, in a controlled way, the interplay between the fundamental

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[3] Published in Nemeth, D., Janacsek, K., & Fiser, J. (2013). Age-dependent and coordinated shift in performance between implicit and explicit skill learning. Frontiers in computational neuroscience, 7, 147.

mechanisms defining implicit/automatic as well as explicit learning. In the present study, we used a sequential learning paradigm to explore the developmental interaction between human explicit and implicit learning.

Although there are various proposals regarding the age-related developmental changes in late adulthood based on changes in working memory capacity, response selection demands, or the spatial requirement of the task (Bo, Jennett, & Seidler, 2012; Bo & Seidler, 2010; Janacsek & Nemeth, 2013, in the development from childhood to adulthood, there are three major proposals about the development of sequence learning in humans. The first posits that there is no significant change with age in the ability of learning sequences implicitly, in other words sequence-learning is age-invariant (Vinter et al., 2000; Meulemans et al., 1998). According to a second proposal, the developmental pattern of sequence learning across ages conforms to the typical inverted-U shape pattern, with best performance at the age of mid-20s (Fletcher et al., 2000; Maybery et al., 1995; Thomas et al., 2004) corroborating the traditional view of a steady improvement of general cognitive learning abilities until well into adulthood (Craik & Bialystok, 2006). The third proposal is based on the surprising finding that, the basic ability of picking up statistical properties of a presented sequence in an implicit manner is best before 12 years of age and it significantly weakens afterwards as measured by the raw RT difference between the high and low frequency triplets found in a probabilistic sequence learning task (Janacsek, Fiser, & Nemeth, 2012). The results of this study implied a marked decrease in this sensitivity around the age of 12, which is in contrast to both earlier proposals. It is important to notice that contrary to the studies of the previous two proposals, the last study is based not on a deterministic but on a probabilistic sequence learning task, which can measure finer, computationally relevant aspects of the learning process.

Specifically, the Janacsek et al. (2012) study proposed that this discrepancy with classical results might be explained by a shift in the structural development of implicit learning based on two lines of evidence. First, although the raw probabilities of the sensory environment are important for learning and both infants (Aslin et al., 1998; Fiser & Aslin, 2002; Saffran et al., 1996; Saffran et al., 1999) and adults (Fiser & Aslin, 2001; Hunt & Aslin, 2001) are highly sensitive to these probabilities, there is an ongoing debate on how using these simple probabilities can lead to a highly complex knowledge of the world, such as sensory invariances and development of a language (Gomez & Gerken, 1999; Marcus et al., 1999; Nemeth & Janacsek, 2011). Recent studies proposed that using an internally stored structured model of the world that emerges based on past experience together with probabilistic learning could help to address this issue and also provide evidence that humans might implement such a strategy during implicit learning (Orban et al., 2008; Tenenbaum, Kemp, Griffiths, & Goodman, 2011). In this framework, as the internal model develops, past experiences become more influential, and therefore, internal interpretations of events become more elaborate and less directly related to their raw occurrence probabilities experienced momentarily. There is ample evidence for both internal model dependent and independent learning in human and animals (O'Doherty et al., 2004; Packard & Knowlton, 2002), and a recent study argued that from a normative standpoint, existence of such multiple learning mechanisms in the brain (cf. model-free vs. model-based learning) with an uncertainty–based arbitration between them would be computationally optimal (Daw et al., 2005). Anchoring this hypothesis biologically, it has been suggested that the presumed mechanisms related to model-free and model-based learning were related to the basal ganglia vs. the prefrontal areas and temporal lobe of the cortex, respectively (Daw et al., 2005).

The second line of evidence provides support for the separated, complementary and also competitive nature of the prefrontal- and medial temporal lobe (MTL)-dependent learning based on internal models vs. basal ganglia-dependent model-free learning. Various studies investigating learning under specific conditions showed that obstructing the PFC and/or MTL by a demanding secondary task (Foerde et al., 2006) do not adversely affect implicit learning. Other studies found that inserting a task between the learning sessions (R. M. Brown & Robertson, 2007a, 2007b), performing a working memory and an implicit learning task simultaneously (Filoteo, Lauritzen, & Maddox, 2010), or a neuropharmacological blockage (Frank et al., 2006) even had a positive effect on performance in an implicit learning task. Moreover, a recent study found that hypnosis boosted implicit statistical sequence learning by three times, presumably caused by the disconnection of the frontal lobe from other brain areas, reducing the competition between brain systems (Nemeth, Janacsek, Polner, & Kovacs, 2013). Importantly, it is known that the cortical areas connected to the internal models related to model-based learning become truly functional late in the development, around the age of 12 (Blakemore & Choudhury, 2006; Giedd et al., 1999), which is about the age at which Janacsek et al. (2012) found the sudden decrement in sensitivity to the relative raw probabilities.

Based on these two lines of evidence, Janacsek et al. (2012) proposed that the emerging functionality at around 12 signals the shift when the system adapts efficiently to more complex aspects of the world by relying more on internal model-based interpretations, while somewhat neglecting the raw probabilities of the sensory input, and therefore, decreasing the ability to develop and stabilize fundamentally new basic competences. Thus in fact, the seemingly paradoxical result of gradually becoming less sensitive to basic statistics, if timed appropriately, could be the optimal strategy for human skill learning in general.

The Alternating Serial Reaction Time (ASRT) Task (Howard & Howard, 1997) is a unique tool to investigate the computational background of this conjecture, because we can measure different processes, which are related more to internal model building or more to model-free learning in the same experimental design. In the ASRT task, participants are asked to respond to stimuli, which appear according to a probabilistic sequence structure (e.g., 2r1r3r4r, where numbers represent specific locations on the screen determined by the sequence, and r represent randomly selected location). Because of this probabilistic structure, we can determine several different or partly different learning measures: triplet learning, statistical learning, higher-order sequence learning, and maximized learning (Howard & Howard, 1997) (see method part). From the point of view of model-free and model-based learning the two prominent types of learning are 1) *Statistical Learning* defined as the differentiation between high and low frequency elements only in randomly appearing stimuli, which makes it possible to measure purely frequency-based learning, and 2) *Higher-order sequence learning* defined as the differentiation between elements appearing in a larger sequential pattern versus appearing randomly when the appearance frequencies of these elements are controlled. Thus *statistical learning* does not require previously built-up representation beyond the detection of relative frequencies of simple repetitive events leading more easily to a model-free type of learning. In contrast, *Higher-order sequence learning* must be based on a more global and complex representation of sequence structure defined by interactions of multiple events one experiences across space and time and therefore, it is related more to model-based processes.

To sum up, it has been hypothesized by Janacsek et al. (2012) that the cognitively controlled processes coming online at around 12 are useful for more targeted explicit learning at the cost of becoming relatively less sensitive to raw probabilities of events. To test this hypothesis, we collected data in an ASRT sequence learning task using probabilistic sequences in five age groups from 11 to 39 years of age, replicating the original implicit learning paradigm in an explicit task setting, where participants were guided to find repeating sequences, and compared it to the original implicit learning task. With the help of this experimental design, we could draw the developmental differences separately for statistical learning of raw probabilities and for more complex, higher-order sequence learning. Moreover, by analyzing the course of learning across the task in more detail, we were able to characterize the development of model-based processes across ages and conditions (explicit vs. implicit) more specifically.

Methods

Participants

There were 288 participants in the experiment, between the ages of 11 and 39, that were clustered into five age groups between 11-13, 14-15, 16-18, 19-29 and 30-39 years of age (Table 2.2.1). Half of the participants took part in the explicit condition and half in the implicit condition (some results of the latter data were already published in the paper of Janacsek et al., 2012). None of the participants suffered from any developmental, psychiatric or neurological disorders. All participants gave signed informed consent (parental consent was obtained for children) and received no financial compensation for participation. The study was approved by the National Psychological Ethical Committee of Hungary.

Condition	Age group	Age	Sex	Education
Explicit	11-13-year-old (n=23)	11.35 (0.71)	11 M / 12 F	5.13 (0.34)
	14-15-year-old (n=23)	14.87 (0.34)	12 M / 11 F	7.91 (0.29)
	16-18-year-old (n=38)	17.00 (0.40)	13 M / 25 F	10.63 (0.67)
	19-29-year-old (n=43)	21.30 (2.02)	26 M / 17 F	14.49 (1.74)
	30-39-year-old (n=20)	35.10 (3.21)	11 M/ 9 F	15.55 (2.42)
Implicit	11-13-year-old (n=24)	11.58 (0.65)	16 M / 8 F	4.64 (0.73)
	14-15-year-old (n=21)	14.71 (0.46)	13 M / 8 F	7.95 (0.67)
	16-18-year-old (n=24)	17.04 (0.36)	12 M / 12 F	10.45 (0.52)
	19-29-year-old (n=45)	21.71 (3.01)	29 M / 16 F	14.98 (2.42)
	30-39-year-old (n=27)	34.78 (2.21)	14 M/ 13 F	17.44 (3.53)

Table 2.2.1. Demographic data and mean RT in the different groups. In all columns, numbers in parentheses show standard deviation.

Task and Procedure

Learning was measured by the ASRT task (Howard & Howard, 1997). In this task, a stimulus (e.g. a dog's head; Figure 2.2.1A) appeared in one of four empty circles on the screen and participants had to press the corresponding button when it occurred. The computer was equipped with a special keyboard with four heightened keys (Y, C, B, and M on a Hungarian keyboard; equivalent to Z, C, B, M on a US keyboard), each corresponding to the circles in a horizontal arrangement. The task was presented in blocks with 85 stimuli: the first five button pressings were random for practice purposes, then an 8-element alternating sequence (e.g., 2r4r3r1r, where each number represents the one of the four circles on the screen and r represents a randomly selected circle) repeated ten times. The response to stimulus interval was 120 ms (Nemeth et al., 2010; Song, Howard, & Howard, 2007).

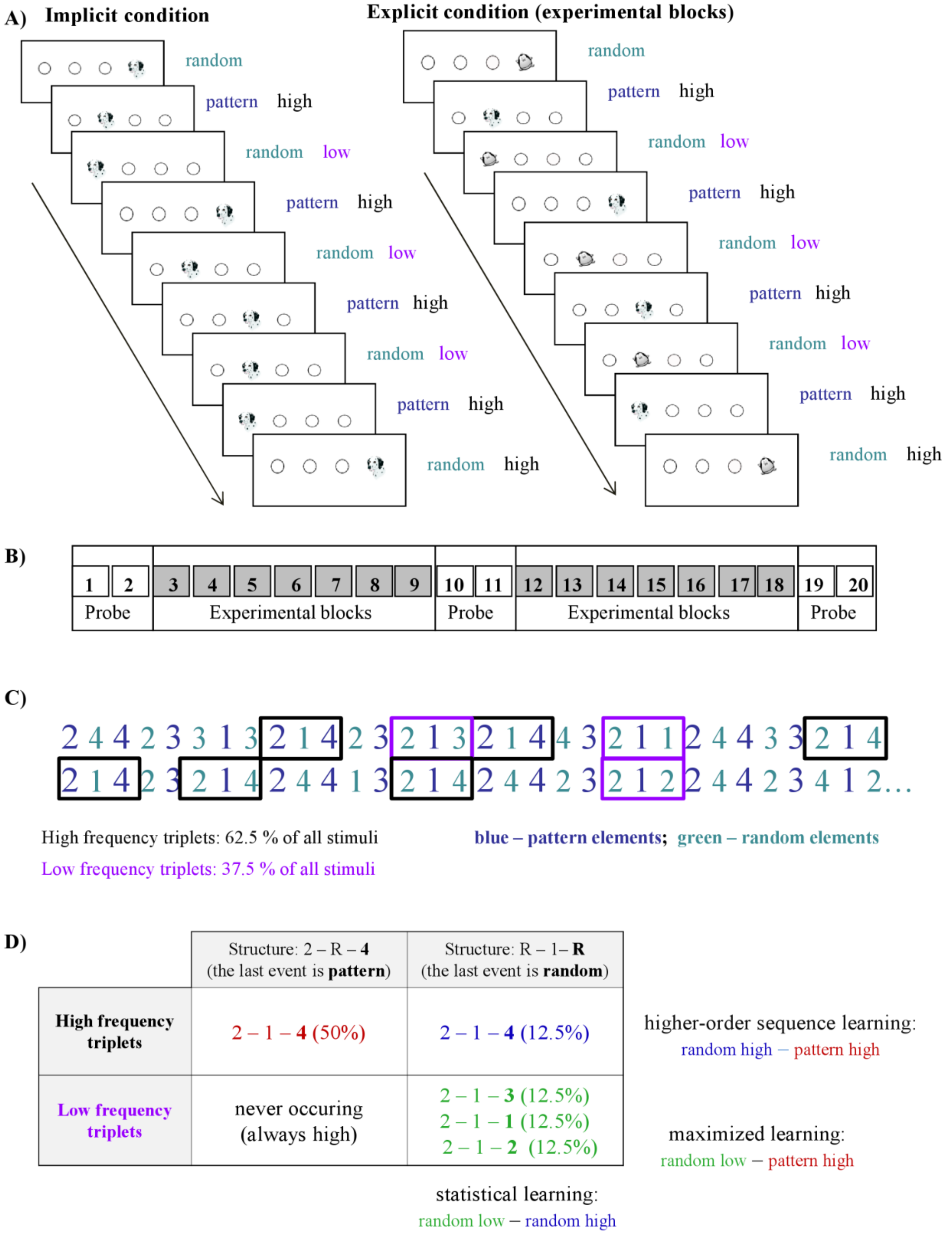

Figure 2.2.1. **Design and learning measures in the study. A)** An implicit and an explicit version of the ASRT task were administered in the experiment. In the explicit version of the task (right panel), the regularity was marked by using different stimuli for sequence elements (a dog's head) and for random ones (penguin). In the implicit condition (left panel), sequence and random elements were not marked differently (a dog's head was used always). **B)** There was a total of 20 blocks in the study: Block 1-2, 10-11 and 19-20 were called "probe blocks" in which all sequence elements were marked with the same picture (a dog's head), while the underlying structure of the sequence was the same as in the remaining blocks, "the experimental blocks" where an explicit marking denoted the random (penguin) and pattern elements (dog). **C)** As the ASRT task contains an alternating sequence structure (e.g., 2r4r3r1r, where numbers correspond to the four locations on the screen and the r represents randomly chosen locations), some runs of three consecutive elements (called triplets) occur more frequently than others. For subsequent analyses, we determined for each stimulus whether it was the last element of a high-frequency triplet (black frames) or low-frequency triplet (purple frames). **D)** We assessed *pure statistical learning* (see text) by comparing the responses for those random elements that were the last elements of a high frequency triplet, opposite to those that were the last of a low frequency triplet (right column). In contrast, *higher-order sequence learning* was assessed as a difference between responses for pattern elements (which are always high frequency triplets) vs. random-high frequency triplet elements (top row). The additive effect of statistical and higher-order sequence learning is called *maximized learning* in our study (upper left vs. lower right cells).

An implicit and an explicit version of the ASRT task were administered in the experiment. In the *implicit version* of the task, participants were informed that the main aim of the study was to find out just how extended practice affected performance on a simple reaction time task. Therefore we emphasized performing the task as fast and as accurately as they could. They were not given any information about the regularity that was embedded in the task (Nemeth et al., 2010). In the *explicit version* of the task, the regularity was marked by different stimuli for sequence and random elements (cued experimental blocks - Song, Howard, & Howard, 2007). In order to maintain the attention and motivation of the children we chose pictures of animals to indicate sequence (a dog's head) and random (a penguin) elements (Figure 2.2.1A). Participants were informed that penguin targets always had randomly chosen locations while dog targets always followed a predetermined pattern. They were instructed to find the hidden pattern defined by the dog heads in order to improve their performance, thus to be faster and more accurate using this sequence information to predict the sequence elements.

The ASRT consisted of 20 blocks. As one block took about 1-1.5 minutes, the task took approximately 20-30 minutes. In the explicit condition, Blocks 1-2, 10-11 and 19-20 were *probe blocks* (Figure 2.2.1B), where sequence and random elements were not indicated (dog's head was used for all stimuli). In these probe blocks participants were not told that there would be any regularity in the sequence, although the same regularity was included as the one in the cued blocks. Although our study focuses on experimental blocks, the main aim of inserting the probe blocks was to be able to compare the performance in implicit and explicit conditions more directly utilizing the fact that in these blocks neither group was informed about the regularity.

Explicit knowledge about the sequence was measured after each cued block in the explicit condition. Participants were instructed to report any regularity they noticed and the experimenter registered their answers. This method allowed us to determine the duration (in term of the number of blocks) participants needed to learn the sequence correctly as defined by consistently reporting the same sequence from that point on in the remaining blocks. In the implicit condition, participants were not asked to report the regularity after each block because this instruction would have made them focus on finding the regularity, thus it would eliminate the instruction differences between the two conditions. Rather, to determine the amount of explicit knowledge the participants acquired about the task in the implicit condition, a short questionnaire was administered after the experimental session (Song et al., 2007). 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-point scale where 1 denoted "Nothing noticed" and 5 denoted "Total awareness". Importantly, none of the participants in the implicit condition, children or adult, reported noticing the hidden repeating sequence.

For each participant, one of the six unique permutations of the 4 possible ASRT sequence stimuli was selected in a pseudo-random manner, so that the six different sequences based on a permutation rule were used equally often across participants (Howard & Howard, 1997; Nemeth et al., 2010).

The stimulus structure in the ASRT task

We will discuss two important aspects of the statistical structure defined by our ASRT sequences. We define *long-range correlations* to refer to all statistical dependencies due to correlations coming from adjacent and non-adjacent co-occurrences not between the elements of three consecutive locations in the sequence, i.e. triplet, but the element of the triplet and some preceding other elements. These correlations are strongly related to the predetermined sequences of the task. In addition, we define *local structures* as statistical relations coming from all other statistical regularities but not from the predetermined sequence structure.

Regarding the local sequence structures, in the alternating sequence structure of our ASRT task (e.g., 2r4r3r1r), some triplets (i.e. combinations of three consecutive events) occurred more frequently than others. Importantly, there are two different ways how such frequent triplets could occur. For example, in the above illustration, 2_4, 4_3, 3_1 and 1_2 (where "_" indicates the middle element of the triplet) occurred often, and they did so either by the third element (bold numbers) being derived from the sequence or so that it was a random element. In contrast, infrequent triplets could occur only in one way. Specifically, 1_3 or 4_1 triplets occurred less frequently only so that the third element was random (Figure 2.2.1C and 2.2.1D). Following previous studies, we refer to the former as *high-frequency triplets* and the latter as *low-frequency triplets*. Note that due to the higher occurrence probability, the final event of high-frequency triplets was more predictable from the initial event of the same triplet compared to the low-frequency triplets (also known as non-adjacent second-order dependency (Remillard, 2008). To quantitatively assess the effect of these differences in occurrence probabilities on learning, for each stimulus/event, we determined whether it was the last element of a high- or low-frequency triplet providing one independent factor of the learning process (Figure 2.2.1D).

The second aspect of the statistical structure of the ASRT sequences is defined by the long-range correlations, the dependencies beyond the triplet that are due to the four non-adjacent elements following a preset sequence. This effect can be quantified by noticing that triplets with the last element being "random" have strong correlations between the middle element of the triplet and the elements preceding the triplet. In contrast, triplets with "pattern" last element have such correlations only with elements further away from the beginning of the triplet. The effect of this difference in distance-dependent correlations on human performance is unknown. Nevertheless, the dichotomy between pattern- and random-last triplets provides the second independent factor in our design to understand what drives skill learning (columns of Figure 2.2.1D). To quantify the effects, first we have calculated the relative probabilities of these different triplet types and found that out of the 64 possible triplets in the task (4^3, 4 stimuli combined for three consecutive events), 16 are high frequency triplets, each of them occurring in approximately 4% of the trials, about 5 times more often than the low-frequency triplets. Thus, approximately 62.5 % of all trials are high-frequency triplets and the remaining 37.5 % of trials are low-frequency ones, while out of the 62.5 % of the high-frequency triplets 50% and 12.5% are pattern-last and random-last triplets, respectively (Figure 2.2.1D). Note, that each trial (i.e. presentation of a stimulus) is defined exclusively either as the last element of a high- or a low-frequency triplet based on the n-2 trial (Howard & Howard, 1997; Janacsek et al., 2012).

Results

Learning types in the ASRT task

Previous ASRT studies used several methods for analyzing learning in the ASRT task. The first option is to measure the overall difference between responses for pattern vs. random elements (pattern-random learning; e.g., Howard & Howard, 1997). However, this measure neglects the differences in probabilistic structure of the sequence based on 2-lag non-adjacent second-order dependencies, i.e. the fact that some triplets are more frequent than others. Since it is known that people are sensitive to such probabilistic nature of a sequence by being faster on more frequent triplets compared to the less frequent ones, more recent, studies also compared responses to high and low frequency triplets separately (triplet learning; e.g., Howard & Howard, 1997; Janacsek, et al., 2012). Note however, that this measure still collapses high frequency triplets across random-last and pattern-last triplets (compared the two rows of Figure 2.2.1D). Hence, knowledge about the sequence structure independent of the local statistical features – cannot be extracted from this learning measure alone. To overcome this problem, in some studies an additional learning measure was introduced based on the difference between responses for high frequency pattern-last and high-frequency random-last elements as measured between the two columns of the first row in Figure 2.2.1D (Howard & Howard, 1997; Song et al., 2007). However, a systematic comparison of these measures and clarification of their relation within a single study has not been done before.

To dissect the various effects contributing to sequence learning, we used the measures above and added new statistical measures to assess the amount of pure statistical learning in the ASRT task. We define *pure statistical learning* as the difference in responses between high-frequency and low-frequency random-last triplets (right column, Figure 2.2.1D). In this case, the sequence properties are the same: both are random-last triplets (finishing with a penguin stimulus) the only difference between the two groups being statistical in nature: whether those triplets are more or less frequent. Thus, statistical learning is defined as faster responses for high frequency random elements compared to low frequency ones. Note, that statistical learning measures a different effect than higher-order sequence learning: the first assesses purely the benefit of presentation frequency differences of local elements, while the second one measures the effect of long-range repetitions due to the predetermined multi-element sequence. This means that assuming independence between these two measures, we should see an additive effect of these two types of learning when comparing responses for pattern elements vs. random low frequency elements (*maximized learning*, upper right vs. lower left cells in Figure 2.2.1D) with statistical and higher-order sequence learning results. We tested this hypothesis by calculating and comparing all these learning effects.

In our study, we first report the triplet learning results because this has been the most common analysis method in the ASRT studies and thus it gives us the opportunity to directly compare our results with those of previous studies. Next, we compare the developmental trajectory of statistical and higher-order sequence learning across implicit and explicit conditions between ages of 11 and 39 years, using the above mentioned measures to obtain a more detailed picture about the underlying mechanisms in probabilistic sequence learning tasks.

Triplet learning across age groups and conditions

To compare triplet learning among age groups and conditions, first we conducted a mixed design ANOVA for the *experimental blocks* (as defined in Figure 2.2.1B) with TRIPLET (2: high vs. low frequency) and BLOCK (1-14) as within-subject factors, and AGE GROUP (11-13, 14-15, 16-18, 19-29 and 30-39 years of age) and CONDITION (explicit vs. implicit) as between-subjects factors (Figure 2.2.2). All significant results are reported together with the η^2_p effect size and Greenhouse Geisser ε correction factors where applicable. Planned comparisons and post hoc analyses were conducted by Fisher's LSD pairwise comparisons.

The ANOVA revealed significant triplet learning (indicated by the significant main effect of TRIPLET: $F(1, 278) = 291.55$, $\eta^2_p = .51$, $p < .001$) such that RTs were faster on high than on low frequency triplets. The conditions differed in the extent of this triplet learning (shown by the significant TRIPLET x CONDITION interaction: $F(1, 278) = 37.49$, $\eta^2_p = .12$, $p < .001$): the participants in the explicit condition were 27.66 ms faster on high than on low frequency triplets, while this difference was only 13.12 ms in the implicit condition. Overall, age groups showed similar extent of learning (TRIPLET x AGE GROUP interaction: $F(1, 278) = 1.10$, $\eta^2_p = .02$, $p = .357$); however, there was a trend in the TRIPLET x AGE GROUP x CONDITION interaction ($F(1, 278) = 2.00$, $\eta^2_p = 0.03$, $p = .095$), suggesting different learning performance across age groups in implicit vs. explicit conditions.

Specifically, in the implicit condition, post hoc tests revealed that the 11-13-year-old group exhibited the highest level of triplet learning, differing from all other groups (ps < .069) who performed on the same level between 14 and 39 years of age (ps > .408). In contrast, in the explicit condition, all age groups reached similar extent of triplet learning (ps > .147). Although there was a small advantage in the 14-15-year-old group, this was significantly higher only to the 16-18-year-old group's performance ($p = .037$). Comparing the extent of learning in explicit vs. implicit conditions separately for each age group, the post hoc tests revealed similar level of triplet learning in the implicit and explicit conditions for the 11-13-year-old group (22.53 vs. 25.15, respectively, p = .644). In contrast, other age groups demonstrated higher triplet learning in the explicit condition than in the implicit one (ps < .033).

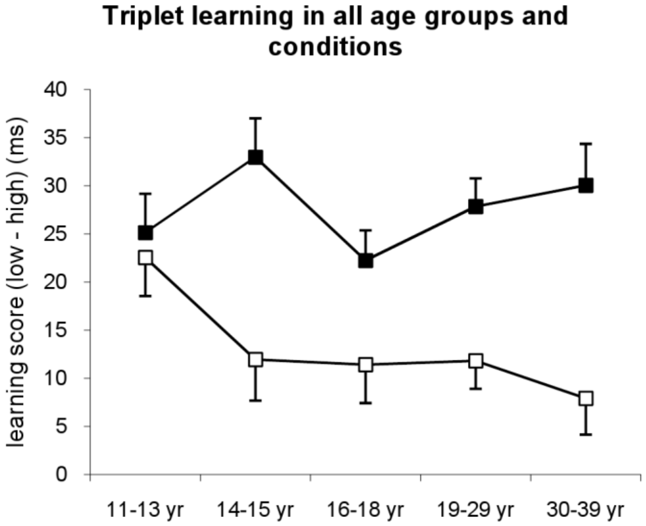

Figure 2.2.2. Triplet learning in all age groups separately for explicit (filled squares) and implicit (open squares) conditions. Learning score was defined as the difference between RTs for low versus high frequency triplets. In the implicit condition, the 11-13-year-old group showed the highest learning differing from all other groups, while in the explicit condition all groups performed at the same level. Error bars represent standard error of mean (SEM).

A similar ANOVA was conducted for the 6 *probe blocks*. The ANOVA revealed significant triplet learning (indicated by the significant main effect of TRIPLET: F (1, 278) = 96.958, η^2_P = .259, p < .001) such that RTs were faster on high than on low frequency triplets. Neither the conditions nor the age groups showed differences in the amount of learning (ps > .248). In sum, this measure revealed that, on average explicit learning of sequences has an advantage over implicit learning at all ages with the exception of the 11-13-year-old-group.

Explicit knowledge across the age groups and conditions

For the explicit condition, we assessed the number of participants in all age groups who gained explicit knowledge about the sequence during the task. The χ^2-test revealed a significantly different distribution across age groups (χ^2 (4) = 18.19, p = .001). In the 11-13-year-old group, only 69.6 % of the participants could report the correct sequence structure during the task while in other age groups, at least 95 % of the participants gained explicit knowledge about the sequence (Figure 2.2.3A).

To further characterize the age differences in the explicit knowledge, we compared when subjects gained their explicit knowledge about the sequence during the experiment. We measured the number of the block where the participants could report the sequence structure consistently (i.e., reported the same correct sequence in all consecutive blocks). A univariate ANOVA (excluding those participants who did not succeed to report the correct sequence structure in the task at all) revealed significant difference among the age groups (F (4, 130) = 7.440, $\eta^2_p = .186$, $p < .001$) (Figure 2.2.3B). Specifically, the mean of the experimental blocks where the 11-13-year-old group reported the sequence consistently was 6.875, significantly differing from all other age groups, typically remaining around 2.83 (ps < .003). All other age groups did not differ significantly from each other (ps > .07). For the implicit condition, we did not ask participants to report the sequence after any block because it would have drawn their attention to the hidden structure of the task eliminating the implicitness of this condition. Instead, we collected a verbal report after the subjects finished the entire experiment, and found that none of them could report the correct sequence structure.

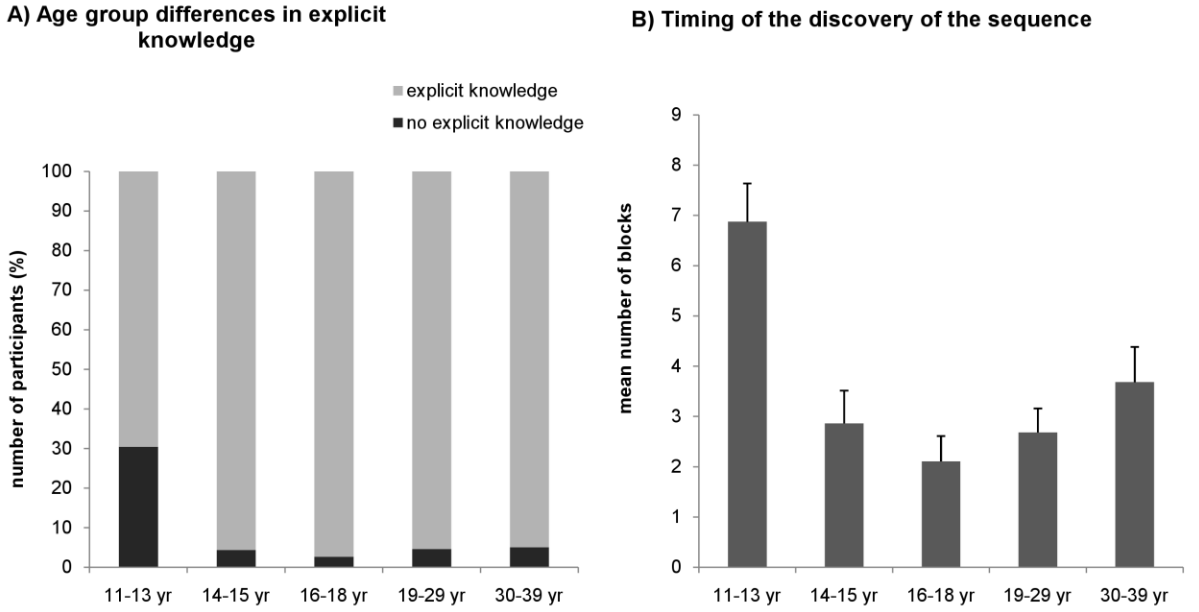

Figure 2.2.3. Results of the verbal reports about the sequence knowledge in the explicit condition. A) Around 30 percent of the participants in the 11-13-year old group could not report the sequence throughout the whole task (black portion of bars) while this percentage was significantly smaller (~ 5%) in all other groups. **B)** Participants in the youngest group who could report the sequence correctly gained this explicit knowledge significantly later (around the 6-7th block) than the older groups. Error bars represent standard error of mean (SEM).

Statistical and higher-order sequence learning across age groups and conditions

To further dissect the nature of learning among age groups and conditions, we conducted a mixed design ANOVA for *experimental blocks* with TYPE (3: pattern, random-high frequency and random-low frequency elements) and BLOCK (1-14) as within-subject factors, and AGE GROUP (11-13, 14-15, 16-18, 19-29 and 30-39 years of age) and CONDITION (explicit vs. implicit) as between-subjects factors. This ANOVA allowed us to disentangle a number of relevant factors influencing sequence learning.

First, the analysis revealed a strong evidence for both statistical and higher-order sequence learning within the general learning effect of this task reported above (Figure 2.2.4). We found a significant main effect of TYPE (F (2, 556) = 122.422, $\eta^2_p = .306$, $p < .001$), suggesting that participants responded differently to pattern, random-high frequency and random-low frequency elements, respectively. Specifically, post hoc test showed that they were the fastest on pattern elements (upper left cell Figure 2.2.1C; 461 ms), differing significantly both from random-high frequency (upper right cell, Figure 2.2.1C; 465 ms, $p = .006$) and random-low frequency elements (lower right cell, Figure 2.2.1C; 481 ms, $p < .001$). Thus, the RT differences between random-high and pattern-high triplets (higher-order sequence learning) as well as between random-low and random-high (statistical learning) were both significant ($p < .001$).

Second, we also found that the extent of these learning effects was different between the implicit and explicit conditions (significant TYPE x CONDITION interaction: F (2, 556) = 33.511, $\eta^2_p = .108$, $p < .001$). In the explicit condition, participants exhibited significant higher-order sequence learning: responses for pattern elements were 13 ms faster than for random-high frequency elements ($p < .001$). In addition, they were significantly faster on random-high elements compared to random low elements, revealing statistical learning (15.81 ms, $p < .001$). The pattern vs. random-low difference was also significant (29 ms, $p < .001$). Surprisingly, in the implicit condition, participants were significantly *slower* on pattern elements compared to random-high elements despite the 4-fold difference in appearance frequency, thus demonstrating a *reversed* higher-order sequence learning (-5.5 ms, $p = .005$). The statistical learning was to a large extent similar to that in the explicit condition ($p = .976$), namely participants were 15.74 ms faster on random-high compared to random low elements ($p < .001$). Due to the reversed higher-order sequence learning, the pattern vs. random low difference (overall learning) in the implicit condition (10 ms, $p < .001$) was significantly smaller compared to the explicit condition ($p < .001$).

Third, investigating the effect of age within the ANOVA design added further detail to the emerging picture, as we found a significant TYPE x CONDITION x AGEGROUP interaction (*F* (8, 556) = 2.936, $\eta^2_p = .041$, *p* = .003). Specifically, in the implicit condition, the 11-13-year-old group exhibited the highest level of statistical learning (Figure 2.2.4A), differing significantly from all other groups (*p*s < .02). The decline was monotonic and the drop was significant from level in the 14-15-year-old group to level in the 18-29-year-old group (*p* = .014). There was a notable lack of such monotonic decrement in learning under the explicit condition, where all age groups showed a similar magnitude of statistical learning (*p*s > .229), suggesting age invariance of such learning.

Comparing the extent of statistical learning in explicit vs. implicit conditions separately for each age group, the post hoc tests revealed stronger statistical learning in the implicit condition than in the explicit one for the 11-13-year-old group (32.29 vs. 14.47 ms, respectively, *p* = .003) (Figure 2.2.4A). In contrast, the 19-29 and 30-39-year-old groups exhibited an opposite pattern by showing higher statistical learning in the explicit (18.05 and 19.90 ms, respectively) than in the implicit condition (4.9 and 9.7 ms, respectively). In the older age group, however, this difference did not reach significant (*p* = .003 for the 19-29-year-old group and *p* = .09 for the 30-39-year-old group). In the adolescent groups, the extent of the statistical learning was similar in both conditions (14-15-year-olds: 13.49 vs. 18.25 for explicit and implicit conditions, respectively, *p* = .438; 16-18-year-olds: 13.14 vs. 13.50, *p* = .947). Taken together, the difference between statistical learning in the explicit and implicit conditions reversed across age groups, children showing stronger learning in the implicit condition while adults demonstrating stronger learning in the explicit condition.

In the case of the higher-order sequence learning (Figure 2.2.4B), the effect of learning was stronger in the explicit than in the implicit condition (*p*s < .045 for all age groups). Analyzing the conditions separately, in the explicit condition, all age groups showed a significant learning effect (*p*s < .03). The extent of this learning was similar in all age groups, except for the 14-15-year-olds who performed slightly but not significantly better than the other groups (*p*s between .056 and .136). In the implicit condition, the RT difference between pattern and random-high elements was not significant between 16 and 39 years of age (*p*s > .397), however, the 11-13-year-olds demonstrated a significant *reversed learning*, being faster on random-high elements compared to the pattern elements (*p* = .01), and the 14-15-year-old group showed a similar albeit non-significant trend (*p* = .106). Neither of these two groups differed significantly from the older groups in learning (*p*s > .107). Thus, summing up the different local patterns, we found a) significant and quasi-age-independent advantage of the explicit condition over the implicit one, b) a significant learning effect in the explicit condition across the board, and c) a significant interference in the youngest subjects in the implicit condition.

We also conducted a correlational analysis to examine the relationship between verbal reports and RT learning measures. We found a significant correlation between the timing of the discovery of the sequence and the extent of higher-order sequence learning (r = -.22, p = .01, corrected for age), such that the earlier the participants could report the sequence structure, the better their higher-order sequence learning performance was in the explicit condition. In contrast, there was no correlation between the verbal reports and the statistical learning measure (r < .1), suggesting that this type of learning is not related on explicit knowledge.

In order to assess the effect of all structures carried by the sequences on learning, one needs to compare the difference between the pattern-high and the random-low conditions (upper left and lower right cells in Figure 2.2.1C). This analysis provides a clear indication of the purely additive effect of statistical and higher-order sequence learning where different parts of the two curves (different age groups) are controlled more strongly by different types of learning (Figure 2.2.4C). For example, learning by the 11-13-year-olds is similar in explicit and implicit conditions (p = .49) and this similarity is determined mainly by larger statistical learning combined with a larger interference in the higher-order learning in the implicit condition compared to an average statistical and higher-order sequence learning in the explicit condition (Figure 2.2.4A-B). In the other age groups, the overall stronger maximal learning in the explicit condition (ps < .019), is driven by the advantage of the explicit condition in both statistical and higher-order sequence learning which is not compensated any more (in fact, enhanced) by the reduced statistical learning advantage and nonexistent learning in the higher-order learning in the implicit condition.

To round up our analysis, a similar mixed-design ANOVA was conducted for the 6 probe blocks of the experiment. This ANOVA revealed a significant main effect of TYPE (F (2, 554) = 27.953, η^2_p = .092, p < .001) due to the RTs with pattern and random high frequency triplets (459.95 ms vs. 458.44 ms, respectively) being significantly faster than that of random low frequency triplets (467.75 ms, ps < .001), with no difference between pattern and random high triplets (p = .274). Neither the Conditions, nor the Age group x Condition interaction reached significance (ps > .207).

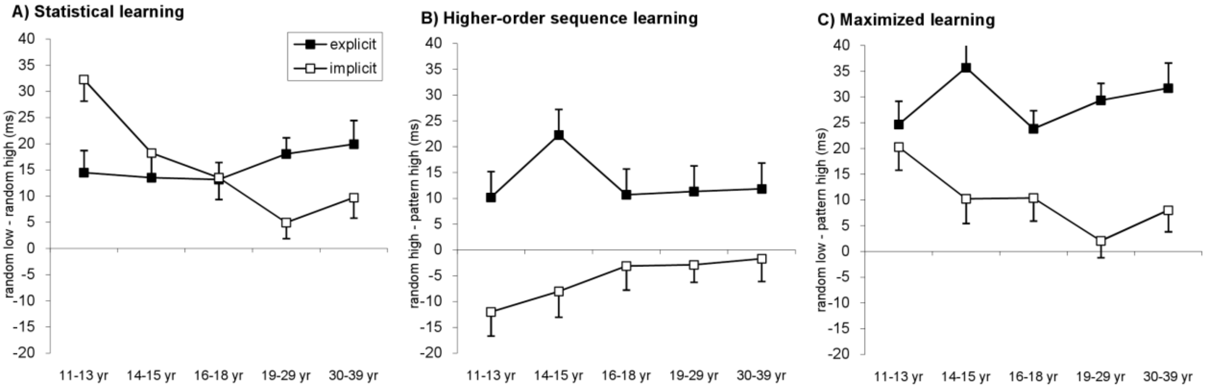

Figure 2.2.4. Detailed analysis of the learning across age groups and conditions. A) Statistical learning (RT difference between random low and random high-frequency triplets) resulted in a gradually declining developmental curve in the implicit condition with an age invariant performance in the explicit condition. The youngest age group exhibited better statistical learning in the implicit condition compared to the explicit one while the opposite pattern was observable between 19 and 39 years of age. **B)** In the case of higher-order sequence learning (RT difference between random high-frequency and patter elements) only groups in the explicit condition showed significant learning, with approximately similar extent of learning across ages. **C)** The additive effect of the statistical and higher-order sequence learning is evident by maximized learning (RT difference between random low-frequency and pattern elements). The pattern is similar to the triplet learning results (cf. Figure 2.2.2): the highest learning of the 11-13-year olds in the implicit condition while mainly similar level of learning across age groups in the explicit condition. Error bars represent standard error of mean (SEM).

Within-block effects on learning across age groups and conditions

We further analyzed our data by splitting each block into two halves, to investigate earlier claims that reactive inhibition emerges within blocks, masking the potential learning effects (Brawn, Fenn, Nusbaum, & Margoliash, 2010; Rickard, Cai, Rieth, Jones, & Ard, 2008). According to these reports, the longer people have to perform a reaction time task arranged in blocks of, for example, several seconds or minutes, the slower they become by the end of each block, and consequently, their performance is the best at the beginning of each block (Brawn et al., 2010; Rickard et al., 2008). Since younger children can be more affected by this kind of fatigue/slow-down, it is important to take this effect into account when comparing learning performances across a wide range of ages. Therefore, we conducted a mixed design ANOVA on *experimental blocks* with TRIPLET (high vs. low frequency), BLOCK (1-14) and PART (first vs. second half of blocks) as within-subject factors and AGE GROUP (11-13, 14-15, 16-18, 19-29 and 30-39 years of age) and CONDITION (explicit vs. implicit) as between-subject factors (Figure 2.2.5A-B).

The ANOVA revealed significant triplet learning overall (main effect of TRIPLET: F (1, 278) = 312.945, $\eta^2_p = .53$, $p < .001$), with higher learning for the explicit condition compared to the implicit one (29 vs. 14 ms; TRIPLET x CONDITION interaction: $F(1, 278) = 35.997$, $\eta^2_p = .115$, $p < .001$). Interestingly, taking the PART of the blocks into account, we found a significant TRIPLET x CONDITION x PART interaction ($F(1, 278) = 7.539$, $\eta^2_p = .026$, $p = .006$): triplet learning was greater in the second part of the blocks compared to the first part for the implicit condition (12.5 vs. 16.5 ms, $p = .032$), while the opposite trend was obtained for the explicit condition (30.98 vs. 27.81 ms, $p = .086$) (Figure 2.2.5). Although the TRIPLET x CONDITION x PART x AGE GROUP interaction did not reach significance ($F(4, 278) = .962$, $\eta^2_p = .014$, $p = .429$), planned comparisons revealed that in the 11-13-year-old group, the triplet learning was greater in the second part of the blocks (27.30 ms) compared to the first part of the blocks (15.98 ms) but only in the implicit condition ($p = .01$). By contrast, in the explicit condition the extent of learning was similar in both parts of the block (25.30 vs. 28.66 ms, $p = .449$). The opposite pattern was observed between 19 and 39 years of age: the extent of learning in the first and second half of blocks was similar in the implicit condition (*p*s > .33), while they exhibited greater learning in the first half of blocks than in the second half in the explicit condition (19-29-year old group: 32.78 vs. 26.36, $p = .049$; 30-39-year old group: 36.59 vs. 24.04 ms, $p = .009$). Between 14 and 18 years of age participants showed similar extent of learning in both parts of the blocks in both conditions (*p*s > .275).

A similar ANOVA was conducted for the 6 *probe blocks*. The ANOVA revealed significant main effect of TRIPLET ($F(1, 278) = 147.602$, $\eta^2_p = .347$, $p < .001$) such that RTs were faster on high than on low frequency triplets. The TRIPLET x PART x AGE GROUP was marginally significant ($F(4, 278) = 2.377$, $\eta^2_p = .033$, $p = .052$). Post hoc tests revealed that the 11-13-year old group exhibited larger triplet learning in the first part of the blocks (21.08 vs. 12.91 ms, $p = .039$) collapsed across conditions, while the opposite trend was observable in the 14-15- and 19-29-year old groups (*p*s < .09). Other interactions regarding the CONDITION and AGE GROUP were not significant (*p*s > .373).

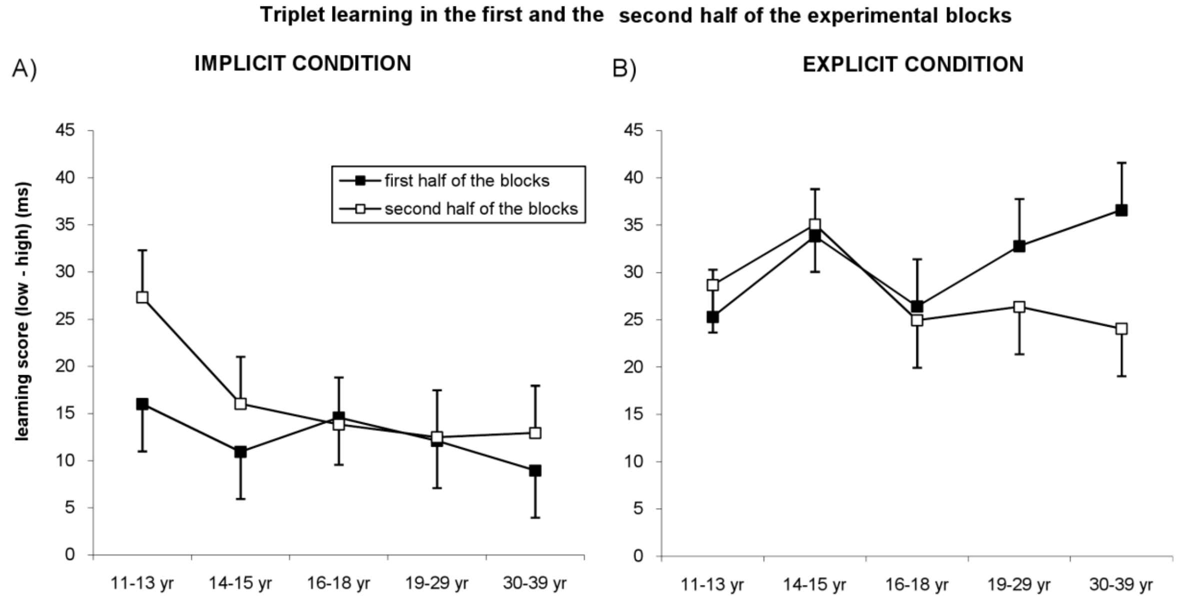

Figure 2.2.5. Triplet learning in the first and second half of the blocks. A) In the implicit condition, the youngest group outperformed the other groups in the second half of the blocks, while they exhibited a similar level of learning in the first half of the blocks. **B)** In the explicit condition, participants between 19 and 39 years of age showed higher learning in the first half of the blocks compared to the second half while other groups exhibited the same level in both parts of blocks. Error bars represent standard error of mean (SEM).

Discussion

There were two main aims of the present study. First, we wanted to obtain a detailed and systematic description of probabilistic sequence learning in both explicit and implicit setups so that this kind of skill-related learning could be related to other types of purely perceptual learning domains such as visual statistical learning (Fiser & Aslin, 2001, 2002, 2005). Second, using the insights of the first aim, we wanted to test the hypothesis that there is a coherent shift in the interaction between simple raw probability-based and complex, internal-model based learning at around the age of 13 (Janacsek et al., 2012). To this end, we investigated the differences of explicit and implicit probabilistic sequence learning in different age groups between 11 and 39 years of age.

To fulfill the first aim, we analyzed pure statistical vs. higher-order sequence learning separately. In the case of classical triplet analysis used in many previous studies (Howard & Howard, 1997; Janacsek, et al., 2012; Nemeth & Janacsek, 2011; Song et al., 2007), the triplet frequency information (high vs. low frequency elements) was mixed with sequence information (random vs. pattern elements), making the interpretation difficult and fuzzy. With our new analysis methods, we could factorize the problem of triplet learning and clarify the nature of the underlying learning mechanisms. We quantified pure statistical learning as the difference in reaction time to high and low probability random events (random-low minus random-high frequency triplets, Figure 2.2.1D) independent of the long-range sequence information. In contrast, we measured higher-order sequence learning by RTs capturing the difference between the ability to internalize a triplet on its own vs. the same triplet embedded in a repetitive larger structure (random-high minus pattern-high frequency triplets, Figure 2.2.1D) while the simple statistical information about the elements within the triplets is equated. Hence our *statistical learning* is a measure of acquiring knowledge of the local statistical structures (individual appearance probabilities), while higher-order sequence learning is a measure of becoming sensitive to long-range relational structures. Both type of learning is based on the input statistics, but they measure independent aspects of the input structure, and while simple local structures are presumably easier to learn right away, learning global structures might get a serious boost from additional ability to handle more complex memory constructs, which we refer to as the internal models utilized in model-based learning. We also propose that our higher-order sequence learning measure is more closely related to explicit knowledge that is more suited for explicit learning. This proposal has been corroborated by our finding of a significant correlation between the timing of the discovery of the sequence and the extent of higher-order sequence learning in the explicit condition. Notice that no such correlation was detected for statistical learning supporting our view that the simple statistical relationships discovered by this type of learning are more readily subject of model-free learning.

Our first important finding is related to the fact that explicit learning seriously boosts the ability to learn higher-order structures by directly focusing the subjects' attention on the relevant structures in our task (Figure 2.2.4B). Within this analysis, we also found that in the implicit learning setup, learning higher-order structures by younger children is significantly interfered with whereas in older subjects the effect of higher-order structures is approximately zero (Figure 2.2.4B). This provides our first hint that a significant gradual shift occurs in the processing of more complex information of the input around the age of 13, which can be detected in an implicit task.

In the case of *statistical learning*, we found a gradual decline across ages in the implicit condition, contrasting the age invariant learning effect we measured in the explicit condition (Figure 2.2.4A). However, the performance in the explicit condition was inferior to the implicit case around 11-13 year, while it was better beyond the age of 19. It is important to consider two facts in interpreting these results. First, the flat explicit developmental curve does not mean that subjects would perform invariantly in ANY kind of explicit sequential task, only that in the present task, the complex interaction between explicit and implicit processes result in a fairly constant performance. Second, since our explicit measure always combines explicit and implicit learning (i.e. there is no purely explicit learning), the comparison of the implicit and explicit results should always be interpreted in a relative manner, that is how much the explicit learning machinery adds or interferes with the basic implicit learning processes. Thus, while due to their independence, statistical and higher-order sequence learning results can be considered separately and combined additively to obtain the results of maximized learning both for implicit and explicit learning separately (see Figure 2.2.4C), the same kind of independent treatment cannot be applied between implicit and explicit results of either type of (statistical or higher-order sequence) learning. Specifically, the flat explicit learning performance during statistical learning (Figure 2.2.4A) is not an indicator of unchanging ability of extracting explicit knowledge-based information at different ages.

With these two points in mind, our interpretation of the above statistical learning results (Figure 2.2.4A) is that despite the steady decrease of implicit performance with age, subjects manage to keep the overall performance at older ages - as measured in the explicit task- from falling, presumably with the increasing help of learning processes evoke by the explicit information. In other words, young children could pick up raw probability information better if no explicit influence interfered with their implicit processes, whereas this implicit learning ability deteriorated with age but also received a serious boost from explicit-knowledge-based help when the subject was more mature. We propose that the performance in implicit statistical learning is more directly related to the model-free processes mentioned in the introduction, while the addition of explicit information leading to interference in young age and boost in older age in the explicit learning task is related to the contribution of the model-based learning processes that can more effectively extract higher order structures.

The analysis of the explicit knowledge about the sequence structure also supports the idea that the interaction between model-free and model-based processes can explain the pattern of the implicit and explicit learning results: we found that the 11-13 year old group gained explicit knowledge of the higher-order structures slower and less effectively compared to later ages (Figure 2.2.3). Specifically, these results demonstrate that the relationship between model-free and model-based processes (also termed sometimes as the implicit and explicit processes) is of a competitive nature (Poldrack et al., 2001): the less knowledge acquired explicitly on the structure the more implicit learning effect we have.

Returning to *higher-order sequence learning* in the explicit condition, there was a strange peak at ages 14 and 15 around the age where the reversed learning effect appeared in the implicit condition (Figure 2.2.4B). We speculate that these effects might be related to the gradual shift in dominance between purely local statistical and more global higher-order learning suggesting that the underlying computational mechanisms of the two types of learning use fundamentally different and somewhat complementary components. Specifically, at younger age, even higher-order relations are detected with a superior ability to extract raw probability structures, while around the age of 13, the same performance starts to be achieved by a very different strategy relying more on the utilization of explicitly treatable information.

In general, our result and their interpretation provides a very different and more complex picture about the development of human sequence learning compared to the earlier developmental proposals based on age-invariance (Meulemans et al., 1998; Vinter & Perruchet, 2000) or the inverted-U shape curve (Fletcher et al., 2000; Maybery et al., 1995; Thomas et al., 2004). We propose that a) there are multiple learning processes playing parts in sequence learning, namely model-free and model-based learning, b) in simple model-free learning tasks based on raw probabilities of events, young children are superior compared to adults, c) for learning more complex types of patterns, model-based learning develops somewhat later at around 13 year of age, d) incorporating model-based features into overall learning interferes, by definition, with the superior sensitivity to raw probabilities of model-free learning, and e) nevertheless, the overall ability to learn all sorts of tasks in our environment improves with the integration of the model-based learning component.

To understand more thoroughly the developmental curve of sequence acquisition, it is worthwhile to consider memory processes such as reactivation and reconsolidation in these types of tasks (Rickard et al., 2008; Walker, Brakefield, Seidman, et al., 2003). During the acquisition of sequences we are learning, recalling and reactivating the sequence elements continuously. Recalling or reactivating a previously consolidated memory makes it fragile and susceptible to interference once again, therefore requiring periods of reconsolidation (Walker, Brakefield, Seidman, et al., 2003). These repetitions of the recall, reactivation and consolidation processes allow a continuing refinement and reshaping of previously learned motor or cognitive skills in the context of ongoing experience. In experimental designs (fingertapping or SRT tasks) and partly in real-life situations, we are learning sequences arranged in blocks, which are separated by shorter or longer time periods. Several recent studies showed that the separate analysis of the different parts of the learning blocks is crucial in understanding the consolidation and reconsolidation of sequence learning (Brawn et al., 2010; Nemeth, Janacsek, Király, et al., 2013; Rickard et al., 2008). In particular, in the beginning of the blocks we have to recall and reactivate the sequence structure partly learnt already in the previous blocks. The second part of each block might be responsible for the reconsolidation of the sequence structure. In our study, we found that this "detection of probabilities - reactivation/recall – reconsolidation" cycle is different across ages and conditions: while in the implicit condition the learning of the second half of the blocks is better than the learning in the first half of the blocks in younger ages, in the explicit condition an opposite pattern emerged with better performance in the first half of the blocks in older ages (Figure 2.2.5). These results suggest that the memory reactivation processes are weaker before early adolescence in the implicit condition, presumably because of the weaker model-based processes. However, when subjects have an efficient cue to find the hidden structure in the explicit condition, it can boost the model-based processes as reflected in the similar extent of learning in the first and second half of the blocks, but only after 16 year of age. In older ages the reactivation of the previously acquired knowledge is more effective in the explicit condition, with a weaker performance in the second half of the blocks (Figure 2.2.5B). These results can be connected to fatigue effect caused by a more attention demanding explicit learning because this effect disappears in the implicit condition where cognitively controlled processes are less dominant.

Although we focused on experimental blocks in this study, we also administered probe blocks in order to investigate the transfer of the acquired knowledge from the more controlled learning situation to a more automatic one. Our results showed that although all groups exhibited learning in these probe blocks, the gain of explicit instructions diminished in most cases, suggesting that this amount of learning is not enough to build a deeper representation about the sequence structure. In other words, in spite of whether or not the participants were able to form some type of internal representation of the sequence structure, this learning was not enough to generate an automatic, procedural behavior. This could be the reason for failing to find developmental differences in these probe blocks.

To sum up, the present study provides additional support for the developmental framework proposed in Janacsek et al's (2012) study: there is a shift in early adolescence when the system adapts efficiently to more complex aspects of the world by relying more on internal model-based interpretations, while somewhat neglecting the raw probabilities of the sensory input. The results also corroborates the findings that the cortical areas implied in storing the internal models for model-based learning become truly functional late in the development, around early adolescence (12-14 years of age; Blakemore & Choudhury, 2006; Giedd et al., 1999). In addition, by separating the different components of sequence learning, our results could also demonstrate the competitive interaction between simple model-free and more complex model-based memory processes (Logothetis et al., 2012; Nemeth, Janacsek, Polner, et al., 2013; Poldrack et al., 2001). Finally, these results build a bridge between the classical domain of procedural skill learning and the more perceptual-type statistical learning literature raising the possibility that despite obvious differences, these processes share partially the same computational bases.

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2.3 Boosting probabilistic learning[4]

Abstract

Human learning and memory depend on multiple cognitive systems related to dissociable brain structures. These systems interact not only in cooperative but sometimes competitive ways in optimizing performance. Previous studies showed that manipulations reducing the engagement of frontal lobe-mediated explicit, attentional processes could lead to improved performance in striatum-related procedural learning. In our study, hypnosis was used as a tool to reduce the competition between these two systems. We compared learning in hypnosis and in the alert state and found that hypnosis boosted striatum-dependent sequence learning. Since frontal lobe-dependent processes are primarily affected by hypnosis, this finding could be attributed to the disruption of the explicit, attentional processes. Our result sheds light not only on the competitive nature of brain systems in cognitive processes, but also could have important implications for training and rehabilitation programs, especially for developing new methods to improve human learning and memory performance.

Keywords: memory systems, hypnosis, sequence learning, functional connectivity, prefrontal cortex, striatum

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Human learning and memory rely upon multiple cognitive systems related to separable brain structures. These systems interact in cooperative and sometimes competitive ways in optimizing memory and information processing performance (Brown & Robertson, 2007a; Poldrack et al., 2001; Poldrack & Packard, 2003). Support for the competitive nature of memory systems comes from studies showing interactions between explicit/hypothesis-testing and implicit/procedural systems (Ashby, Alfonso-Reese, Turken, & Waldron, 1998; Daw et al., 2005; Matilla-Duenas et al., 2012; Poldrack & Packard, 2003; Seger & Cincotta, 2005). The former is often characterized by voluntary mechanisms relying more on attentional resources, and thought to be mediated by frontal and medial temporal lobe (MTL) structures, while the latter relies more on automatic, nonconscious processes mediated primarily by striatum. Manipulations reducing the engagement of the explicit, hypothesis-testing system, such as a demanding secondary task (Foerde et al., 2006; Fu & Anderson, 2008; Matilla-Duenas et al., 2012), a distractor task inserted between the learning sessions (Brown & Robertson, 2007a), or neuropharmacological blockage (Frank et al., 2006) had no effect or even led to performance improvements in striatum-dependent learning tasks. In a recent study, Galea, Albert, Ditye and Miall (2002) also found improvements in procedural learning after the disruption of the dorsolateral prefrontal cortex (PFC) using theta burst stimulation. In contrast, strengthening the reliance on explicit, hypothesis-testing processes resulted in impaired procedural learning (Fletcher et al., 2005; D. V. Howard & Howard, 2001) with greater PFC activity during the acquisition (Fletcher et al., 2005).

As rapid and reversible changes of cognitive processing are encountered in hypnosis, this phenomenon is an excellent tool of research in the cognitive neurosciences (Egner, Jamieson, & Gruzelier, 2005; Fischer, Nitschke, Melchert, Erdmann, & Born, 2005). Regarding the neural background of hypnosis, studies demonstrated that people (especially with high susceptibility) show decreased performance on some frontal lobe-related tasks in hypnosis (Kallio et al., 2001; Kaiser et al., 1997; Peigneux et al., 2006). More recent studies suggest reduced functional brain connectivity between cortical areas in hypnosis, and this is especially typical for frontal areas (Fingelkurts, Kallio, & Revonsuo, 2007; Oakley & Halligan, 2009). Hypnosis temporarily disconnects certain frontal areas from the anterior cingular cortex and other brain areas, disturbing the frontal attentional control and executive system (Egner et al., 2005; Gruzelier, 2006; Kaiser, Barker, Haenschel, Baldeweg, & Gruzelier, 1997).

In our experiment, we used hypnosis as a tool to reduce the competition between frontal lobe-related explicit, hypothesis-testing and striatum-related procedural-based systems. In order to measure procedural learning in the hypnotic and alert states, we administered a motor sequence acquisition test, which is based on statistical learning mechanisms (J. H. Howard, Jr. & Howard, 1997; Perruchet & Pacton, 2006). This fundamental learning mechanism underlies not only motor but also cognitive and social skills (Kaufman et al., 2010; Lieberman, 2000; Nemeth et al., 2011; Romano Bergstrom et al., 2012; Ullman, 2004); it is therefore an important aspect of life from infancy to old age. Sequence learning is essential for learning languages and operating appliances, such as, for example computers and musical instruments (D. V. Howard et al., 2004; Romano Bergstrom et al., 2012). Social skills appear in compound behaviors realized in proper sequences activated under appropriate circumstances. Most models and empirical studies of sequence learning highlight the role of the basal ganglia (Dennis & Cabeza, 2011; Okihide Hikosaka et al., 1999; O. Hikosaka et al., 2002; Keele et al., 2003; Kincses et al., 2008; Rieckmann et al., 2010).

The main question of the study was how the disruption of frontal lobe functions by hypnosis affects performance in procedural-based sequence learning. Sequence learning was measured by the Alternating Serial Reaction Time (ASRT) task (Howard and Howard 1997) on highly hypnotizable young adults. Participants performed the ASRT task both in waking alert and hypnotic state. In addition, executive functions were assessed by the Wisconsin Card Sorting Test (Heaton et al. 1993; Anokhin et al. 2010) and Verbal Fluency Task (Spreen and Strauss 1991) in order to investigate the possible interactions between frontal lobe functions and the effect of hypnosis on sequence learning.

Methods

Participants

Fourteen healthy, right-handed students from the University of Szeged participated in the experiment (12 females; mean age: 22.70, SD: 1.70; mean years of education: 15.50, SD: 1.58). All participants provided signed informed consent. They received no financial compensation for participating in the study. The study was approved by the Psychology Ethics Committee at the University of Szeged, Institute of Psychology.

Participants were selected from a pool of pre-tested subjects, on the basis of their hypnotic susceptibility. Hypnotizability was measured using the Hungarian version of the Harvard Group Scale of Hypnotic Susceptibility: Form A (HGSHS:A, Shor, Orne, & Press, 1962). Scoring procedure was based on the original English version (scores ranging from 0 to 12). Similarly to previous studies (Halsband, 2006; Kallio, Revonsuo, Hämäläinen, Markela, & Gruzelier, 2001) we defined high hypnotizability as having 8 or higher score on the

HGSHS:A. The mean hypnotizability score of the participants was 9.07 (SD = 0.997; range from 8 to 12).

Tasks

Sequence learning task - The Alternating Serial Reaction Time Task (ASRT) is a widely used paradigm measuring implicit sequence learning in cognitive neuroscience (Song et al., 2007b). In this task, stimuli appear in one of four empty circles on the screen and participants are required to press the corresponding key (Y, C, B, M on Hungarian keyboard) as quickly and accurately as possible. Participants are told that stimuli appear randomly, but, in fact, stimuli delivered in a random order (low predictability) alternate with the same stimulus items which, however, follow a regular presentation order (high predictability). Reaction times (RT's) to the high predictability stimuli become shorter than to the low predictability items as participants (implicitly) learn the hidden sequence.

The current ASRT task consisted of one practice block with random stimuli, and 15 blocks with the alternating pattern described above. The latter blocks consisted of 85 key presses - the first five button pressings were random for practice purposes, then an eight-element alternating sequence (e.g., 2r1r3r4r, where numbers represent specific stimuli and r represents a random stimulus) was repeated ten times. The response to stimulus interval (RSI) was 120 ms. Participants were given different sequences in the two conditions (see below) in order to eliminate inter-session learning effects.

Fluency task – In this task, participants are instructed to produce as many words belonging to the same category (animals, supermarket) as possible in 60 seconds, without repetitions, synonyms, or generated forms of the same word (Spreen & Strauss, 1991). The average number of correct words was used as the performance score. Higher score reflects better frontal lobe functions (Baldo, Schwartz, Wilkins, & Dronkers, 2006).

Wisconsin Card Sorting Test (WCST) – This task is one of the most specific tests of prefrontal functions (Anokhin, Golosheykin, Grant, & Heath, 2010; Heaton, Chelune, Talley, Kay, & Curtiss, 1993). Participants are required to derive a correct card sorting rule based on a trial-by-trial feedback. As the rule changes without warning, the participant has to modify the previously learned response strategy on the basis of the feedback information. A key indicator of cognitive flexibility is the number of perseverative errors that occur when the participant persists in using the old strategy despite the negative feedback. A lower number of perseverative errors indicate better frontal lobe functions.

Design and procedure

All tests were conducted on an individual basis. Participants performed the ASRT task in both the alert waking and the hypnotic state, with the same standard instructions. The order of the two conditions was counterbalanced across participants. The delay between the two sessions was 30 days. Fluency and WCST task was administered once, in a third session in alert state. Two participants did not take part in the third session due to time schedule problems.

A skilled hypnotist therapist (the author, Z.A.K.), who has extensive experience with hypnosis, tape-recorded the induction, instructions, and dehypnotizing phases (similarly to Szendi et al.'s study (Szendi et al., 2009)). This recording was played to each participant. The type of hypnosis induction, similarly to that of the hypnotizability scale, was essentially relaxational.

The induction took approximately 14 minutes. After the induction, the hypnosis session began. When participants had completed half of the ASRT task, we played an approximately 30 s long induction in order to maintain their hypnotic state (in the wake condition, subjects had a 30 s rest). In the hypnosis condition, after the task had ended, the dehypnosis instruction was played.

Statistical analysis

As there is a fixed sequence in the ASRT with alternating random elements (e.g., 2r3r1r4r), some triplets or runs of three events occur more frequently than others. For example, following the illustration above, triplets such as 2_**3**, 3_**1**, 1_**4**, 4_**2** occur more often, because the third element (bold numbers) could be both derived from the sequence as well as from a random element. In contrast, triplets such as 4_**1**, 4_**4** would occur infrequently, because in this case, the third element could only come from the random stimuli. Following previous studies (e.g. D. V. Howard et al., 2004; Song et al., 2007b), we refer to the former as high-frequency triplets and the latter as low-frequency triplets. Because of this difference in the occurrence frequencies of certain triplets, after observing two stimuli, a certain third stimulus can be expected with 62,5% of probability (for example, 22*3* is five times more probable than 22*1* or 22*2* or 22*4*). In our analysis, we determined for each stimulus whether it was a more or a less probable continuation for the previous two stimuli. Participants gave faster responses to the more probable than to the less probable stimuli, thus revealing sequence learning in the ASRT paradigm (D. V. Howard et al., 2004; Song et al., 2007b). In addition, general skill learning can be observed in the ASRT task in the overall increase of the response speed, irrespective of the triplet type. Thus, we were able to separately measure sequence-specific and general skill learning in the ASRT task.

Similarly to previous studies (e.g. D. V. Howard et al., 2004; Nemeth, Janacsek, Londe, et al., 2010; Song et al., 2007b), 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 participants often show pre-existing response tendencies to them (D. V. Howard et al., 2004; Soetens et al., 2004). By eliminating these triplets, we could ascertain that any high- versus low-frequency differences were due to learning and not to pre-existing tendencies.

Since the participants' accuracy remained very high throughout the test (as is typical, the average was over 92% for both conditions; (J. H. Howard, Jr. & Howard, 1997; Nemeth, Janacsek, Londe, et al., 2010), we focused on RT for the analyses reported. We calculated medians for correct responses only, separately for high- and low-frequency triplets and for each participant and each third of the stimulus blocks (1-5, 6-10 and 11-15). To compare sequence learning between hypnosis and alert condition, and between groups with high and low executive functions, we conducted repeated measures and mixed design analyses of variance (ANOVAs) with LSD post hoc tests. We reported the relevant effect sizes: η_p^2 for main effects and interactions, and Cohen's d measures for post hoc tests.

Results and Discussion

A repeated measures ANOVA was conducted with TRIPLET (2: high vs. low), BLOCK (3: 1-5, 6-10 and 11-15) and CONDITION (2: alert and hypnosis) as within-subjects factors. In this ANOVA, a significant main effect of TRIPLET reflects sequence-specific learning, which can increase with practice (TRIPLET x BLOCK interaction), while a significant TRIPLET x CONDITION interaction indicate differences in sequence-specific learning between the hypnosis and alert conditions.

ANOVA revealed significant sequence-specific learning (main effect of TRIPLET: $F(1,13)=16.21$, $p=0.001$, $\eta_p^2=0.55$), which increased with practice (TRIPLET x BLOCK interaction: $F(2,26)=9.36$, $p=0.001$, $\eta_p^2=0.42$). The two states differed significantly from each other (TRIPLET x CONDITION interaction: $F(1,13)=7.08$, $p=0.02$, $\eta_p^2=0.35$): sequence learning was 2.5-times higher under hypnosis than in the waking alert state (Figure 2.3.1). Independently from sequence learning, general reaction time decreased with practice (main effect of BLOCK: $F(2,26)=4.93$, $p=0.034$, $\eta_p^2=0.27$). Other main effects and interactions were not significant (all p's>0.34), thus the general reaction time was similar in the waking alert and hypnotic state (main effect of CONDITION: F(1,13)=0.12, p=0.73, η_p^2=0.009). In addition, the rate of sequence learning process was also similar between the two conditions (TRIPLET x BLOCK x CONDITION: F(2,26)=0.42, p=0.63, η_p^2=0.03). Thus, hypnosis affected only sequence-specific learning (the difference between RTs for low and high probability events), and not the general reaction time. As we used a within-subject design with two learning sessions, a further analysis was conducted to test the possible effect of whether hypnosis was in the first or in the second session and ANOVA revealed no order effect on sequence learning.

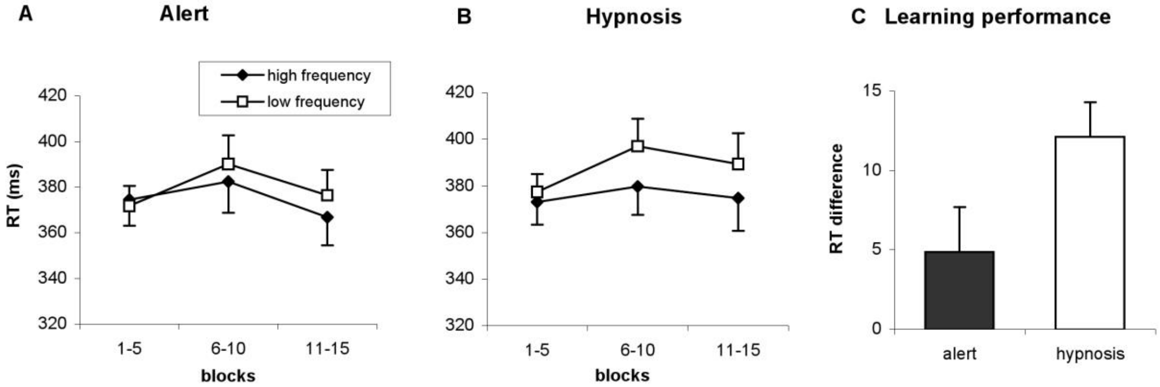

Figure 2.3.1. Sequence learning across blocks is plotted for waking alert (A) and hypnotic state (B), separately. Sequence learning performance (measured by the reaction time differences between high- and low-predictability events) was higher in the hypnotic state compared to the waking alert condition (C). Error bars represent standard error of mean.

To calculate a composite score for executive function, first we transformed measures of fluency task and WCST into z-scores. Then, we averaged these two transformed data into a composite score. Based on the median of this composite measure, we assigned half of the participants to the higher and other half to the lower executive function group. To compare sequence learning between the high- and the low-executive-function groups, in the alert and the hypnosis conditions (see Figure 2.3.2), a mixed design ANOVA was conducted with TRIPLET (2: high vs. low), BLOCK (3: 1-5, 6-10 and 11-15) and CONDITION (2: alert and hypnosis) as within-subjects factors and GROUP (2: high vs. low executive function) as a between-subject factor.

The general reaction time was similar in the two groups (main effect of GROUP: F(1,10)=1.5, p=0.25, η_p^2=0.13), and it was not affected differently by the two conditions

(CONDITION x GROUP interaction: F(1,10)=0.71, p=0.42, η_p^2=0.07). The TRIPLET x CONDITION interaction almost reached the significance (F(1,10)=4.5, p=0.06, η_p^2=0.31) replicating that participants exhibited greater sequence learning under the hypnosis condition compared to the waking alert condition. The overall sequence learning was similar in the high and low executive function groups (TRIPLET x GROUP: F(1,10)=3.07, p=0.11, η_p^2=0.24). Although the TRIPLET x CONDITION x GROUP interaction did not reach significance (F(1,10)=1.72, p=0.219, η_p^2=0.15), the LSD post hoc tests revealed that participants with higher executive functions showed smaller sequence learning in the waking alert state compared to the hypnotic condition (Figure 2.3.2C; p=0.03, d=0.94), while participants with lower executive functions showed similar extent of sequence learning (Figure 2.3.2E; p=0.58, d=0.25). In addition, the learning performance of the high executive function group was significantly smaller compared to the low executive function group in the waking alert state (p=0.04, d=1.31), while it was similar in the hypnotic state (p=0.51, d=0.396).

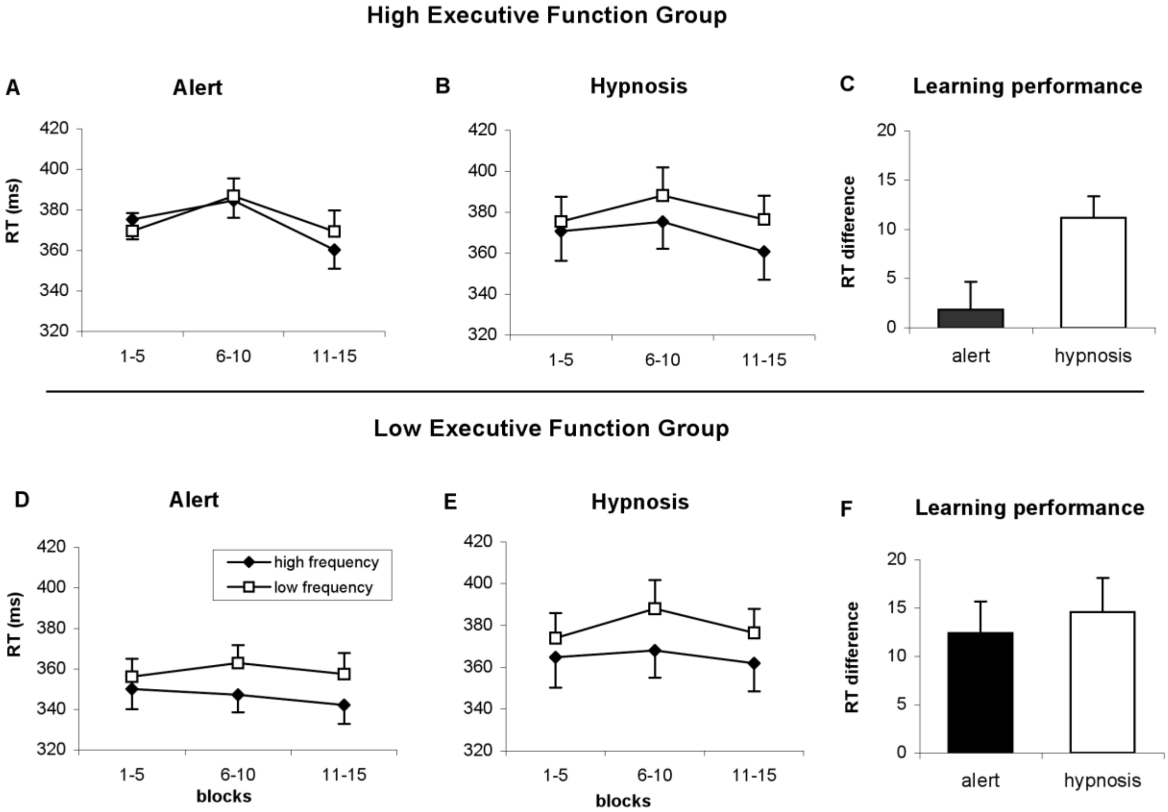

Figure 2.3.2. Relationship between high vs. low executive functions and the effect of hypnosis on sequence learning. Sequence learning across blocks for the high executive function group in waking alert (A) and hypnotic state (B), as well as sequence learning across blocks for the low executive function group in waking alert (D) and hypnotic state (E) is plotted. Participants with high executive functions showed smaller sequence-specific learning

(measured by reaction time differences between high and low probability events) in the alert state compared to the hypnosis condition (C), while participants with lower executive functions showed similar extent of sequence learning in the waking alert and hypnotic state (F). Error bars represent standard error of mean.

Taken together, we found enhanced sequence learning performance in hypnosis. Our results provide support for the idea that learning and memory processes may not only involve the engagement of specific neuroplastic mechanisms, but may also rely upon the disengagement of interacting systems (Brown & Robertson, 2007a, p. 149). Our finding is in line with previous studies demonstrating that manipulations reducing the reliance on frontal lobe-dependent processes improved procedural-based learning performance (e.g., Matilla-Duenas et al., 2012; Seidler et al., 2002).

The improved sequence learning in hypnosis could be attributed to the disruption of attentional control and executive system (Kaiser et al., 1997; Kallio et al., 2001; Peigneux et al., 2006) by weakening the engagement of the frontal lobe and/or the interconnectivity between related brain areas (Egner et al., 2005; Fingelkurts et al., 2007; Gruzelier, 2006; Oakley & Halligan, 2009). This could diminish the competition between two fundamentally incompatible modes of learning: 1) PFC/MTL-mediated hypothesis-testing, attention-dependent processes vs. 2) basal ganglia-dependent procedural learning (Henke, 2010; Matilla-Duenas et al., 2012; Poldrack et al., 2001). Reducing the reliance on executive, hypothesis-testing processes could have improved sequence learning capacity by heightening the sensitivity to statistical probabilities, which is essential for automatic, procedural mechanisms (Daw et al., 2005). This interpretation is consistent with the result that participants with better executive functions showed decreased sequence learning in the waking alert condition compared to the participants with lower executive functions, suggesting that in the alert state relying more on attentional processes prevented the learning of statistical contingencies to a greater extent (P. C. Fletcher et al., 2005). In the hypnotic state, participants with higher executive functions shifted from relying on frontal lobe-related attentional processes to automatic, procedural-based mechanisms, resulting in enhanced sequence learning. However, future neuroimaging studies need to corroborate these results providing direct evidence for the underlying brain systems.

In sum, we found that hypnosis substantially boosted procedural-based sequence learning. This result sheds light not only on the competitive nature of brain systems in cognitive processes, but also could have important implications for training and rehabilitation programs, especially for developing new methods to improve human skill learning.

Acknowledgements

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2.4 Neuropsychological investigation of the relationship between frontal lobe functions and probabilistic sequence learning[5]

Abstract

Implicit sequence learning is a fundamental mechanism that underlies the acquisition of motor, cognitive and social skills. The relationship between implicit learning and executive functions are still debated due to the overlapping fronto-striatal networks. According to the framework of competitive neurocognitive networks, disrupting specific frontal lobe functions, such as executive functions, increases performance on implicit learning tasks. The aim of our study was to explore the nature of such a relationship by investigating the effect of long term regular alcohol intake on implicit sequence learning. Since alcohol dependency impairs executive functions, we expected intact or even better implicit learning in patient group compared to the healthy controls based on the competitive relationship between these neurocognitive networks. To our knowledge, this is the first study to examine the long-term effects of alcohol dependency both on implicit learning and executive functions requiring different but partly overlapping neurocognitive networks. Here we show weaker executive functions but intact implicit learning in the alcohol dependent group compared to the controls. Moreover, we found negative correlation between these functions in both groups. Our results confirm the competitive relationship between the fronto-striatal networks underlying implicit sequence learning and executive functions and suggest that the functional integrity of this relationship is unaltered in the alcohol dependent group despite of the weaker frontal lobe functions.

Keywords: implicit learning, procedural memory, frontostriatal network, competitive brain networks, executive functions

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Introduction

As the number of patients with alcohol problems have been continuously growing over the past years, it is important to discover both its short and long-term effects. Studies have shown that almost half of the patients have residual deficits measured by explicit neuropsychological tests even after the third abstinent week furthermore 15% of the patients experience these deficits even after a whole year (Zinn, Stein, & Swartzwelder, 2004). However, the exact impact of alcohol on implicit cognition is still vaguely known. Implicit non-conscious learning and memory processes are crucial in several aspects of daily life such as everyday routine behaviors, motor, cognitive and social skills. Therefore the present paper focuses on how alcohol dependency affects implicit learning processes.

Deeper insight into how alcohol directly affects certain brain structures might reveal a great deal of its long-term effects. Functional imaging has showed that subjects with alcohol dependency had decreased prefrontal cortical grey and white matter volumes compared to control subjects (Bellis et al., 2005; Pfefferbaum, Sullivan, Mathalon, & Lim, 1997). Right, left, and total thalamic, brainstem, right and left cerebellar hemispheric, total cerebellar, and cerebellar vermis volumes did not differ between groups. These findings suggest that a smaller prefrontal cortex is associated with early-onset drinking problems. Similar findings have also shown the vulnerability of these areas (Medina et al., 2008), thus it seems that the prefrontal region is highly affected by long-term alcohol consumption and it is the most pronounced region in the brain to do so. Such declines in the prefrontal area can cause the greatly explored deficits in executive processes for alcohol dependent patients (Goldstein et al., 2004).

Working memory refers to the mechanism during which one can online modulate information available within a certain amount of time and capacity. The original working memory (WM) model by Baddeley and Hitch (A. D. Baddeley & Hitch, 1974) proposed two main parts: the phonological loop and the visuospatial sketchpad. Some years later the central executive was also added as a new component responsible for information manipulation mechanisms such as updating, inhibition and shifting (A. D. Baddeley, 1996). Measuring the decline in the central executive part of WM is a good measure of prefrontal deterioration, as it is a process which is critically involved in a number of more complex cognitive behaviors (N Cowan, 1999). A number of experiments have shown that the acute use of alcohol has an impact on the functioning of WM in a way that reduces the available capacity for information to be processed within a certain time-frame (Curtin, Patrick, Lang, Cacioppo, & Birbaumer, 2001). In line with such results and further elaborating them, Finn and colleagues have come to the conclusion that alcohol intake reduced performance on a backward digit span, but only for participants with a high baseline working memory capacity. Interestingly in a later experiment (Finn & Hall, 2004) based on the forward digit span task, high-span individuals were able to perform just as well while being under the effect of alcohol, as without the intoxication. It is possible that high span individuals have more storage capacity, which is not sensitive to a more robust task such as the forward digit span task, but backward digit span performance does not stay intact due to its complexity. Both the alpha-span task and the Tower of London task resulted in similar performances under similar circumstances, such that the more complex the task gets, the worse the alcohol dependent group responds (Noël et al., 2001). To sum up this line of thought, the more complex a WM task gets the more the central executive part of the model (A. D. Baddeley, 1994) is involved.

In line with previous results Saults and colleagues found that the task complexity mediates how alcohol impacts WM performance (Saults, Cowan, Sher, & Moreno, 2007). In a relatively simple set of span tasks, acute alcohol intoxication had little or no effect on any general WM holding mechanism used to retain multiple concurrent items. On the other hand it had a more pronounced effect on mnemonic strategies that are needed to maintain task items (attention demanding, consciously mediated verbal rehearsal (A. D. Baddeley, Lewis, Eldridge, & Thomson, 1984). To sum up, alcohol affected tasks requiring only concentrated attention (consciously sustained process) compared to less consciously mediated processes.

Both short-term alcohol intake and long-term alcohol dependency have a significant impact on the performance on tasks that require frontal, parietal, temporal or mixed functions. When it comes to memory, both short- and long-term alcohol usage tends to have a temporally stable, but selective effect on implicit and explicit memory processes respectively (Duka, Weissenborn, & Dienes, 2001; Lister, Gorenstein, Risher-Flowers, Weingartner, & Eckardt, 1991). Depending on the type of assessment, participants who were under the influence of a moderate dose of alcohol, performed worse on an explicit stem completion task, while if the same information was acquired implicitly, their performance remained intact. The above mentioned examples all deal with the effects of acute alcohol intake, which can be thought of as an online measurement. Our study therefore focuses on long-term alcohol dependency to see if performance on such cognitive measurements changes over the course of constant alcohol intake.

One of the most widely used task type in measuring implicit cognitive processes is implicit sequence learning (Reber, 1989). Implicit sequence learning underlies the formation of cognitive, social and motor skills and has been mostly related to the basal ganglia (Sefcsik et al., 2009), with an additional governing role of the frontal lobe (Doyon et al., 1997). These areas together form the fronto-striatal-cerebellar circuit, which has been in the focus of experiments aiming to reveal the network which governs implicit sequence learning (Doyon, Bellec, et al., 2009; Henke, 2010; Klivenyi et al., 2012). The way in which implicit sequence learning is related to the mechanisms of the central executive working memory processes is still a topic that is currently being debated due to the possibility of shared capacities (Janacsek & Nemeth, 2015). As our brain has a predetermined capacity with which it can operate with at a certain point in time, some processes can work in parallel by cooperating, while others are competing for the same resources (Albouy et al., 2008; Poldrack et al., 2001). A robust line of research claim that the weaker frontal lobe related functions can lead to an enhanced implicit, procedural learning (Filoteo et al., 2010; Nemeth, Janacsek, Polner, et al., 2013) based on the competition idea (Poldrack et al., 2001).

In sum, long term alcohol usage affects frontal lobe functions such as working memory and executive functions. The effects of long term alcohol usage can give us a better insight into how fronto-striatal based implicit learning and DLPFC based WM/executive functions are related in alcohol dependent patients compared to healthy controls. To our knowledge this is the first study to explore the effects of alcohol-dependency on implicit learning. On one hand the possible outcome of long term alcohol usage might result in weaker implicit learning performance if implicit learning is positively related to working memory and executive functions by sharing the same neural networks (for the debate see (Janacsek & Nemeth, 2015; Nemeth, Janacsek, Polner, et al., 2013)). On the other hand based on the previously mentioned competition idea, namely that weaker frontal lobe functions can lead to better implicit learning (Janacsek & Nemeth, 2015; Poldrack et al., 2001) we predict that long-term alcohol usage has no effect or can even enhance implicit learning performance.

Materials and methods

Participants

Fourteen alcoholic patients (11 male/3 female) and 16 controls (11 male/5 female) participated in the experiment. The alcohol dependent and the control group were matched on age, gender and years of education (Table 2.4.1). The patient group was recruited from the Rehabilitation unit of the Béla Gálfi Kht Hospital. The inclusion criterion for the alcohol-dependent group was to be completely sober at least three weeks prior to the experiment. Past history of alcohol dependency was diverse, still, according to the number of relapses all participants have had at least one relapse (the *mean* of total relapses were 1.43, *SD*: 0.51).

Controls were individuals who did not have active neurological or psychiatric conditions, had no cognitive complaints, demonstrated a normal neurological behavior, and were not taking any psychoactive medications. All participants provided signed informed consent agreements and received no financial compensation for their participation.

	Control		**Alcohol-dependent**		
	Mean	*SD*	*Mean*	*SD*	*p-value*
Age	49.56	10.68	48.50	10.68	.788
Education	2.12	.72	2.07	.83	.851
Digit Span Task	6.27	.90	5.86	1.03	.301
Listening Span Task	3.86	.83	3.11	.69	.021
Counting Span Task	4.15	.94	3.44	.98	.080
Letter Fluency Task	20.82	5.29	14.78	4.76	.006

Table 2.4.1. Means and standard deviations (SD) of age, education (the number refers to the level of education one has: 1-elementary school, 2-high school, 3-college) and performance on Digit Span, Listening Span, Counting Span, and Letter Fluency Tasks for the control and alcohol-dependent group.

Tasks

The alternating serial reaction time (ASRT) task

Implicit sequence learning was measured by the “Catch the dog” version (Nemeth et al. 2010) of the ASRT task (Howard and Howard 1997). In this task, a stimulus (a dog's head) appears in one of four empty circles on the screen and participants have to press the corresponding button as fast and accurately as they can. The computer is equipped with a special keyboard which only contains four heightened keys (Y, C, B, and M on a Hungarian keyboard; equivalent to Z, C, B, M on a US keyboard) which are necessary for responding. These keys correspond to the target circles in a horizontal arrangement.

The appearance of stimuli follows a predetermined order, which stays unknown for the participants throughout the experiment. Stimuli are presented in blocks of 85 stimuli, from which the first five button pressings are random for practice purposes. These are followed by an 8-element alternating sequence (e.g., 2r3r1r4r, where numbers represents the four circles on the screen and 'r' represents random elements), which is repeated ten times in a block. Due to the structure of the sequences in the ASRT task, some triplets or runs of three consecutive events occur more frequently (high frequency triplets) than others (low frequency triplets). For example, in the above illustration, 1_4, 2_3, 3_1, and 4_2 (where "_" indicates the middle element of the triplet) 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_3 or 4_1 would occur less frequently because in this case the third element could only be random. Note that the final event of high-frequency triplets is therefore more predictable from the initial event when compared to the low-frequency triplets [also known as non-adjacent second-order dependency (Remillard 2008)]. Therefore, before analyzing the data we determined whether each item was the last element of a high- or low-frequency triplet.

Overall, there are 64 possible versions of triplets (4^3, 4 stimuli combined for three consecutive events) through the task, from which 16 are high frequency triplets (62.5%), each of them occurring on approximately 4% of the trials, occurring five times more often than the low-frequency triplets. The remaining 37.5% of the remaining trials are low-frequency triplets.

Similar to previous studies (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 participants often show preexisting response tendencies to them (; D. V. Howard et al., 2004; Soetens et al., 2004). By eliminating these triplets, we could ascertain that any high- versus low-frequency differences were due to learning and not to preexisting tendencies.

Previous studies have shown that as people go further in practicing the ASRT task, they respond more quickly to the high- compared to the low-frequency triplets, revealing sequence-specific learning (Howard and Howard 1997; Howard et al. 2004; Song et al. 2007). In addition, general skill learning – general speed-up in the task, irrespective of the triplet types – can also be measured in the ASRT task.

Finally, it is important to note that the task remained implicit for the participants throughout the experiment. According to previous experiments with the ASRT task, even after an extended practice of 10 days, participants are not able to recognize the hidden sequence (Howard et al. 2004).

Digit Span

The Digit Span Task (Isaacs & Vargha-Khadem, 1989; Racsmány, Lukács, Németh, & Pléh, 2005) is a measure of phonological WM capacity. In this task, participants listen to an experimenter reading lists of series of numbers. The lists consist of increasingly longer series of digits which one has to repeat after the experimenter. Participants had to listen to each of these series and repeat them in order to the experimenter. Starting with three-item series a maximum of four trials was presented at each length. If the first three trials at a particular sequence length were correctly recalled, the series length was increased by one. The maximum number of digits (i.e., series length) recalled correctly three times provided the measure of the digit span (a simple number, e.g., 6).

Listening Span

The Listening Span task ((Daneman & Blennerhassett, 1984); for Hungarian version see Janacsek et al. 2009) is a widely used complex working memory measurement. In this task the experimenter reads aloud increasingly longer lists of sentences to the participants who have to judge whether the sentence is semantically correct or not, and recall the last words of the sentences. Participant's working memory capacity was defined as the longest list length at which they were able to recall all the final words.

Counting Span

The Counting Span task (Case, Kurland, & Goldberg, 1982; A. R. Conway et al., 2005; Engle, Tuholski, Laughlin, & Conway, 1999) is a complex working memory task lacking a strong verbal component. Each trial included three to nine blue circles as targets, one to nine blue squares and one to five yellow circles as distractors on a grey background. Participants counted aloud the number of blue circles in each trial, and when finished with the count, they repeated the total number. When presented with a recall cue, participants recalled each total from the preceding set, in the order in which they appeared. The number of presented trials in a set ranged from two to six. A participant's counting span capacity is calculated as the highest set size at which he or she was able to recall the totals in the correct serial order.

Letter Fluency task

The Letter Fluency task is a widely-used task to measure executive functions, moreover the central executive component of the working memory model (A. D. Baddeley, 2006). In this task, participants are instructed to produce as many letters beginning with the same letter ('k' or ‘t’) as possible in 60 seconds, without repetitions, synonyms, or generated forms of the same word (Spreen & Strauss, 1991) for Hungarian version see (Tanczos, Janacsek, & Nemeth, 2013a, 2013b) the average number of correct words was used as the performance score. Higher score reflects better frontal lobe functions (Baldo et al., 2006).

Procedure

The ASRT task was administered in one session. Participants were informed that the main aim of the study was to find out just how extended practice affected performance on a simple reaction time task. Therefore, we emphasized participants to perform the task as fast and as accurately as they could. Participants were not given any explicit or implicit information about the regularity of the sequence that was embedded in the task.

The ASRT consisted of 25 blocks, which took approximately 30–40 minutes. Between blocks, participants received feedback on the screen about their overall reaction time and accuracy, which was followed by a rest of 10 between 20 seconds before starting a new block. The computer program selected a different ASRT sequence for each participant based on a permutation rule, such that each of the six unique permutations of the four possible stimuli occurred. Consequently, six different sequences were used across participants (Howard and Howard 1997; Nemeth et al. 2010).

The digit span task, the listening span task, the counting span task and letter fluency tasks were administered in a second experimental sitting in order to avoid possible confounding effects of the WM/executive function tasks and the implicit sequence learning task.

Statistical analyses

To facilitate data processing, the blocks of ASRT were organized into epochs of five blocks. The first epoch contains blocks 1–5, the second blocks 6–10, etc. (Barnes et al., 2008; Bennett et al., 2007). As participants' accuracy remained very high throughout the test similarly to previous studies (Howard and Howard 1997; Nemeth et al. 2010), we focused on reaction time (RT) for the analyses reported. For RTs, we calculated medians for correct responses only, separately for high and low frequency triplets and for each participant and each epoch. Additionally, to the RTs, we calculated a learning index, which is the difference between the RTs for high and low frequency triplets.

To calculate a composite score for executive function, we first transformed measures of Listening Span, Counting Span and Letter Fluency tasks into z-scores. Then, we averaged these 3 transformed data into a composite score. Based on the median of this composite measure, we assigned half of the participants to the higher and other half to the lower executive function group. Data of executive functions were not available for five participants in the control group. Therefore all participants were included in the first analysis focusing on sequence learning in the ASRT task but the following analyses including the executive functions were run on the restricted sample (control group: n = 11, alcohol-dependent group: n = 14).

Results

Implicit sequence learning

To compare sequence learning between the groups, RTs were analyzed by a mixed design analysis of variance (ANOVA) with TRIPLET (2: high vs. low) and EPOCH (1–5) as within-subjects factors and PATIENT GROUP (alcohol dependent vs. control) as a between-subjects factor. First of all, the main effect of TRIPLET was significant (F (1, 28) = 7.366, $\eta_p^2 = 0.208$, $p = 0.01$), such that participants responded faster to high-frequency than low-frequency triplets, revealing successful sequence-specific learning. The TRIPLET x PATIENT GROUP interaction did not reach significance (F (1, 28) = 0.137, $\eta_p^2 = 0.005$, $p = 0.714$), indicating that there was no difference between the alcohol dependent and the control group in sequence specific learning. The main effect of PATIENT GROUP alone did not reach significance either (F (1, 28) = 2.482, $\eta_p^2 = 0.005$, $p = 0.126$), indicating that the overall RTs of the patient and healthy controls did not differ significantly (Figure 2.4.1).

The main effect of EPOCH was also significant, indicating that participants showed general skill learning (i.e., they became generally faster) as the epochs went on (F (4, 25) = 39.235, $\eta_p^2 = 0.584$, $p < 0.001$). The EPOCH x PATIENT GROUP (F (4, 25) = 0.322, $\eta_p^2 = 0.011$, $p = 0.863$) interaction was not significant, which indicates that the two groups were not differing in general skill learning.

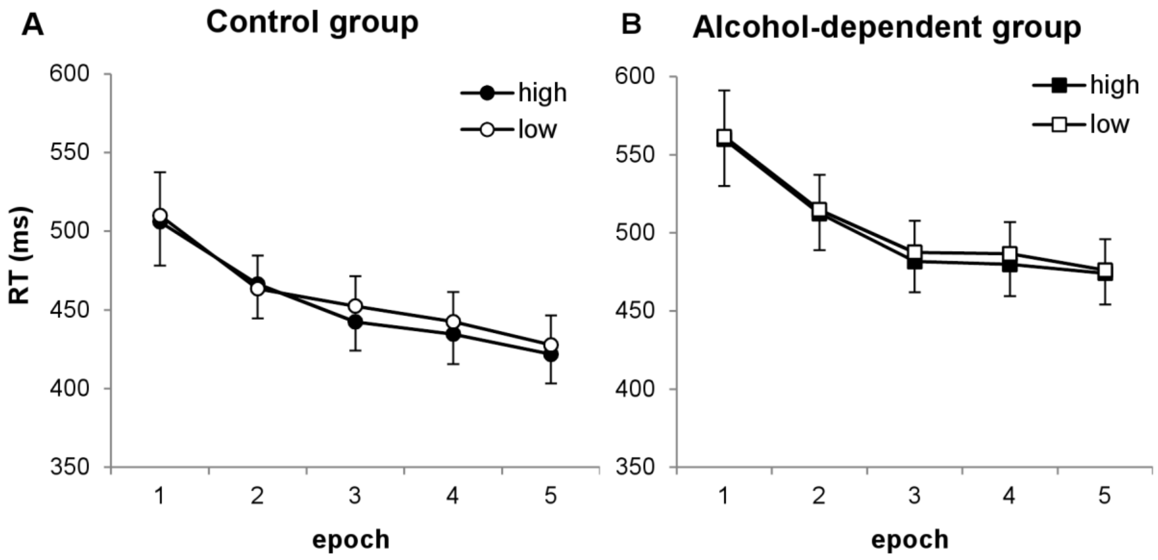

Figure 2.4.1. Reaction times (RTs) in the ASRT Task for the control (A) and the alcohol-dependent group (B). There was no difference between the two groups either in sequence-specific learning (RT difference between high- and low-frequency triplets) or in general skill learning (overall RT improvement across time). Error bars indicate Standard Error of Mean (SEM).

In a following ANOVA we also included EXECUTIVE GROUP (low vs. high) as a between-subjects factor. Here, the TRIPLET x EXECUTIVE GROUP interaction showed a strong trend towards significance (F (1, 21) = 3.988, η_p^2 = 0.160, p = 0.059), indicating that executive functions had an effect on sequence-specific learning in the ASRT task. Participants with lower executive functions showed higher sequence-specific learning compared to the participants with higher executive functions (9.77 vs. 1.87 ms, respectively). Interactions involving both PATIENT GROUP and EXECUTIVE GROUP did not reach significance, suggesting that the level of executive functioning did not have a differential effect in the alcohol dependent and control groups.

Correlations between sequence learning and executive functions

To further explore the relationship between sequence-specific learning and executive functions, we ran correlation analyses for all participants, as well as for the control and alcohol-dependent group separately. We calculated sequence-specific learning measures for the whole session as an RT difference between responses for high and low-frequency triplets for each epoch separately and then averaging these difference scores across epochs. This overall sequence-specific learning score showed a moderate, negative correlation with the executive function scores (r(25) = -0.420, p = 0.037) when the alcohol dependent and the control group was analyzed together (Figure 2.4.2A). Within-group correlations showed similarly moderate, negative correlation in the control group (*r*(11) = -0.499, *p* = 0.118; Figure 2.4.2B), and a relatively strong negative correlation in the alcohol dependent group (*r*(14) = -0.635, *p* = 0.015; Figure 2.4.2C). In addition, we ran further correlation analyses controlling for phonological working memory (measured by the Digit Span task), and found a strong, negative correlation between sequence-specific learning and executive functions in both groups (controls: (*r*(11) = -0.624, *p* = 0.054), alcohol dependent group: *r*(14) = -0.630, *p* = 0.021). Importantly by comparing the two correlations measured on independent groups of subjects, the difference of correlations for the patient group and the healthy controls did not reach significance (Z = -0.492, *p* = 0.622). Thus, these correlation analyses further strengthen the results found in the ANOVA, in that participants with lower executive functions tend to exhibit higher sequence-specific learning.

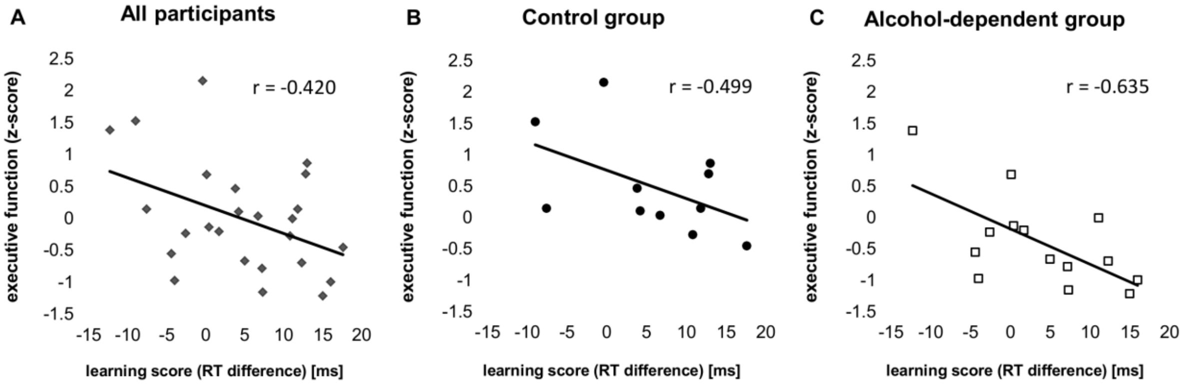

Figure 2.4.2. Relationship between sequence-specific learning and executive functions. There was a moderate to strong negative correlation between these measures for all participants (A), as well as in the control (B) and alcohol-dependent group (C) separately. Thus, weaker executive functions correlated with better sequence-specific learning performance.

Discussion

Our main goal was to investigate how relatively long term alcohol usage might impact implicit sequence learning, and whether executive functions can modulate it. We found that the alcohol dependent and the control groups did not differ in sequence specific learning and general skill learning performance. Moreover we found an inverse relationship between sequence specific learning and executive functions - such that participants with lower executive functions showed higher learning performance in both alcohol dependent and control groups.

Since the long-term effects of alcohol usage on implicit sequence learning are unknown to date, we compared our results to studies manipulating with acute alcohol intake only. In line with previous results on how alcohol impacts implicit processes (Duka et al., 2001; Kirchner &

Sayette, 2003), one explanation for the intact implicit sequence learning can be such that the learning process does not rely on the same frontal circuits as executive functions do, and therefore it is not affected by alcohol consumption. Kirchner and colleagues (2003) differentiated between the automatically and conceptually driven aspects of an implicit task. Their main finding showed a dissociation between these two aspects in a way that alcohol intake had a significant effect on the conceptually driven aspect while it had no impact on any of the automatically driven processes. Thus, acute alcohol intake has a more clear impact on explicit/more executive like processes, while its effects on implicit processes are either not present or are still unknown (Duka et al. 2001). The above mentioned literature is also in line with researchers proving that implicit learning processes are spared during Korsakoff syndrome (Fama, Pfefferbaum, & Sullivan, 2006; Oudman, Van der Stigchel, Wester, Kessels, & Postma, 2011), which is a chronic disorder often caused by long term alcohol dependency, affecting mainly the hippocampus and frontal areas of the brain.

Further interpretations involve that alcohol not only leaves frontal areas intact that are crucial for implicit sequence learning, but the related fronto-striatal-cerebellar network as well. Until now, no experiments have yet proven that alcohol has a significant effect on implicit processes related to the striatum. According to our results, alcohol not only leaves implicit learning intact, but has a definite effect on frontal/executive functions showing a dissociation between processes that mainly rely on frontal capacities (executive functions) compared to processes rely on the striatum (implicit sequence learning). Importantly, further studies need to explore the role of these functional brain networks with neuroimaging methods more accurately. Here we showed a negative relationship between implicit sequence learning and executive functions. The background of such a relationship can be explained by the competition between two learning mechanisms, namely the PFC/MTL-mediated hypothesis-testing attention-dependent processes versus the striatum-dependent less attention-dependent, procedural learning (Filoteo et al., 2010; Henke, 2010; Poldrack et al., 2001). In line with our results studies showed that weakening the interconnectivity between frontal lobe and other brain structures, moreover disruption of the frontal lobe engagement can improve sequence learning (Filoteo et al. 2010). For example a recent finding of Nemeth and others (2013) is in line with this idea demonstrating that manipulations reducing the reliance on specific frontal lobe-dependent processes can improve procedural based learning performance (Filoteo et al., 2010; Galea, Albert, Ditye, & Miall, 2010). One such manipulation can be hypnosis, a tool which temporarily disconnects certain frontal areas from the anterior cingular cortex and other brain areas, disturbing the frontal attentional control and executive system (Egner et al., 2005;

Gruzelier, 2006; Kaiser et al., 1997). This temporal disconnection might be a key factor in the improvement in implicit sequence learning (Nemeth et al. 2013), as it is possible that it eliminates certain frontal areas that would compete for the same capacity. Such a process results in heightened sensitivity to statistical probabilities, which is essential for automatic procedural mechanisms (Janacsek et al. 2012). This interpretation is consistent with the result that participants with better executive functions showed decreased sequence learning in the waking alert condition, due to a possible competition for the same frontal capacities (Nemeth et al. 2013). However if this disruption is present for a longer period of time – which is the case with alcohol dependency – and the brain gets irreversibly degraded, implicit learning processes can also become impaired due to the damage to fronto-striatal networks.

The above mentioned literature shows that the question of how implicit processes and working memory/executive functions are related is still under debate (Janacsek & Nemeth, 2013, 2015). One way to resolve this problem is by noting that not all working memory and executive functions can be localized to only frontal regions (Carpenter, Just, & Reichle, 2000), furthermore that it is possible that the striatum plays a role in WM/executive functions by modulating the inhibition of the PFC (Ashby, Turner, & Horvitz, 2010). Therefore, if alcohol blocks mainly frontal capacities, it is also possible that it does not have such a pronounced effect on all WM processes. This could also be a reason for intact implicit processes, or even implicit performance increases due to the blocking of certain frontal areas by TMS (Galea et al. 2010) or by other tools (Frank et al. 2006; Nemeth et al. 2013). We believe that our results are not due to the storage component of the working memory but more related to the executive functions because after controlling for storage capacity, the negative relationship between implicit sequence learning and complex WM index even became stronger.

The rehabilitation of patients with alcohol problems is a very challenging process as these people have to cope with a number of cognitive deficits, such as problems with memory, attention and so on. Determining the impaired brain networks involved in cognitive processing is extremely helpful in predicting the progress of cognitive decline, as well as for later recommendations for learning strategies and trainings. If we know which functions stay intact while others show a decrement due to the dependency, we can also determine the functions upon which therapies and compensating strategies can be built on. Since implicit learning is involved in acquiring new skills, and it is a cognitive process which seemingly stays intact even after long-term alcohol usage, it can be one of these foundation stones. Also, implicit learning strategies are also involved in the process of habit change, which is essential for changing one's drinking habits.

To our knowledge, the present study is the first to investigate whether long term alcohol usage affects implicit sequence learning, and how these indices correlate with performance on executive functions. We found weaker executive functions, but intact implicit learning in the alcohol dependent group. Thus in spite of the common expectation that alcohol disrupts most cognitive functions we showed that at least one function specifically implicit sequence learning is intact. Our results shed light on the different or partly overlapping fronto-striatal networks that have a different role in implicit processes and executive functions moreover showing a competitive relationship among them.

Acknowledgements

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2.5 Perceptual and motor factors of implicit probabilistic learning learning[6]

Abstract

Implicit skill learning underlies not only motor but also cognitive and social skills, and represents an important aspect of life from infancy to old age. Earlier research examining this fundamental form of learning has demonstrated that learning relies on motor and perceptual skills, along with the possible role of oculomotor learning. The goals of the present study were to determine whether motor or perceptual cues provide better prompts to sequence learning and to remove the possibility of oculomotor learning during the task. We used a modified version of the probabilistic ASRT task, which allowed the separation of motor and perceptual factors. Our results demonstrated that motor and perceptual factors influenced skill learning to a similar extent.

Keywords: implicit skill learning; motor learning; perceptual learning; ASRT; oculomotor learning

Introduction

Implicit skill learning occurs when information is acquired from an environment of complex stimuli without conscious access either to what was learned or to the fact that learning had occurred (Reber, 1993). In everyday life, this learning mechanism is crucial for adapting to the environment and to evaluate events. The most important models of skill learning in cognitive neuroscience and neuropsychological studies emphasize the role of the basal ganglia and the cerebellum (Doyon, Bellec, et al., 2009; Okihide Hikosaka et al., 1999; O. Hikosaka et al., 2002), while the role of the hippocampus remains inconclusive (Albouy et al., 2008; Schendan et al., 2003). Skill learning can be differentiated into phases (an initial rapid phase and a subsequent slower phase), into types (motor, visuo-motor or perceptual such as visual, auditory, etc.), and into consciousness types (implicit and explicit) (Doyon, Bellec, et al., 2009). Implicit motor skill learning tasks have been used for decades, but there is no agreement about how these tasks reflect motor versus perceptual learning, and what their proportions are.

The most widely used task to measure skill learning is the SRT (Serial Reaction Time) task (M. J. Nissen & Bullemer, 1987). In this task, the stimulus appears in one of four possible

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[6] Published in Nemeth, D., Hallgato, E., Janacsek, K., Sándor, T., & Londe, Z. (2009). Perceptual and motor factors of implicit skill learning. *Neuroreport, 20*(18), 1654-1658.

positions on the screen and the subject has to press the appropriate response key as fast as possible. The stimuli follow a predefined sequence, and although the research subjects are not aware of this, they perform better on these trials than in corresponding random trials. In most SRT tasks, the location of the stimulus corresponds with the location of the response key. Therefore, learning can be influenced by the sequence of stimuli locations on the screen (perceptual learning), by the correct answer button sequence in the egocentric space (answer-based learning) or by the finger movement patterns (effector-based learning) (Remillard, 2003).

Another disadvantage of these paradigms (classical SRT and finger-tapping tasks) is that after a short training session, the subjects often recognize the stimulus pattern, which causes significant limitations in studying implicit learning (J. H. Howard, Jr. & Howard, 1997). In contrast, using the Alternating Serial Reaction Time (ASRT) Task (J. H. Howard, Jr. & Howard, 1997) allows researchers to overcome this aforementioned problem by employing an eight-element sequence, whereby random elements alternate with sequence elements (e.g.: 2-R-3-R-1-R-4-R, where R refers to random).

In these research paradigms, it is difficult to isolate perceptual learning. Specifically, motor learning cannot be eliminated in both observation- and transfer-based studies because it is the motor response reaction time that gives the informative measurements (Dennis, Howard, & Howard, 2006). Perceptual learning in these paradigms can be observed only if it can be demonstrated in addition to implicit skill learning. For example, Robertson and Pascual-Leone (2001) showed that if perceptual and motor sequences are combined (e.g., color and location) it leads to a greater level of learning than either one of the sequences alone.

In the case of first-order probability sequences, motor learning is not necessary to learn patterns. However, in second-order probability sequences (e.g., ASRT), perceptual learning is, at best, minimal (Remillard, 2003). Nevertheless, previous studies have been able to isolate perceptual learning based on second- or higher-order probability sequences (Deroost, Coomans, & Soetens, 2009). For example, Dennis and colleagues (2006) found that young adults showed implicit skill learning in higher-order sequences even without motor learning. Moreover, if no motor response was requested, deterministic sequence learning (e.g., SRT) led to explicit learning by simply observing the stimuli, whereby subjects revealed the hidden sequence explicitly (J. H. Howard, Jr. & Howard, 1997; Willingham, Nissen, & Bullemer, 1989). In the case of second-order sequences, explicit knowledge has been shown to be minimal or totally eliminated (J. H. Howard, Jr. & Howard, 1997). Song et al. (2008) demonstrated perceptual learning using similar task and found that learning took place even without a motor response to the observed stimuli. After the observation, subjects were able to transfer the sequence knowledge to the testing (motor) condition. The concern with this study was that the stimuli appeared on four different areas of the screen. Hence, skill learning could have reflected oculomotor learning as well (e.g. Song et al., 2008). The question remains whether learning is purely perceptual when it is accompanied with eye movements. Remillard (2003) found that perceptual learning was not influenced by the distance between the stimuli (i.e., the amplitude of the eye-movement). On the other hand, Willingham and colleagues (1989) were not able to show perceptual learning without eye movements.

Willingham, Wells, Farrel and Stemwedel (2000) changed the conditions of the SRT task after the learning phase in one of the two following ways: either the stimulus sequence (perceptual information) remained the same as in the learning phase while the sequence of the answers (motor information) was changed, or the motor response sequence remained the same and the response locations changed (subjects had to answer crossing their hands during the testing phase). Subjects were able to transfer their knowledge only if the sequence of response locations was maintained, not the sequence of finger movements (Willingham et al., 2000). These findings suggest that the sequence of response locations must have been retained in order for implicit knowledge to transfer, whereas the contribution of motor and perceptual information was less considerable. It is important to note that Willingham and colleagues (Willingham et al., 2000) did not eliminate the possibility of oculomotor learning since the sequence occurred perceptually in the locations of the stimuli.

The goal of the present study was to investigate the role of perceptual learning in implicit sequence learning through a modified ASRT task. In this modified paradigm, the sequence followed a second-order regularity that eliminated the possibility of oculomotor learning because the stimuli always appeared in the same, central position. Similar to the Willlingham et al. (2000) study in the learning phase, the sequence of stimuli and their responses were different. In the second phase (testing or transfer phase), the sequence of stimuli (perceptual information) remained the same and the response sequence (motor information) changed or vice versa.

Our hypothesis was that, unlike Willingham et al. (2000), we would be able to show perceptual learning or perceptual transfer with a task that eliminated oculomotor learning. In addition, our goal was to create a task that would distinguish between perceptual and motor factors of implicit sequence learning.

Methods

Participants – Thirty-four healthy right-handed subjects took part in the experiment. Half of the subjects were randomly assigned to the Perceptual condition (mean age=21.76 years, SD=2.02; 7 male/10 female), and the other half were assigned to the Motor condition (mean age=21.76 years, SD=1.64; 8 male/9 female). Subjects did not suffer from any developmental, psychiatric or neurological disorders. All subjects provided signed informed consent agreements and received no financial compensation for their participation.

Task - We used a modified version of the ASRT task (J. H. Howard, Jr. & Howard, 1997), the so-called AS-RT-Race. We created a story about a car race for the task. The stimuli were the left, right, up and down arrows (5 cm long and 3 cm wide), which appeared in the center of the screen. When the stimulus appeared on the screen, it represented the car’s direction. For example, when the subjects saw an up arrow, they had to press the up button on the keyboard to move the car forward, the left button to turn left, and so on. All subjects pressed the keys with their dominant hand.

After the starting block of 85 random presses, they were told that there was a car crash and the steering wheel failed (see Figure 2.5.1A). The car now kept going to the left if they wanted to go straight, but by turning the steering wheel right they could correct this malfunction, and could continue to go straight. Thus subjects had to mentally rotate the arrows (the steering wheel) by 90 degrees to the right, and press the button corresponding to this rotated arrow.

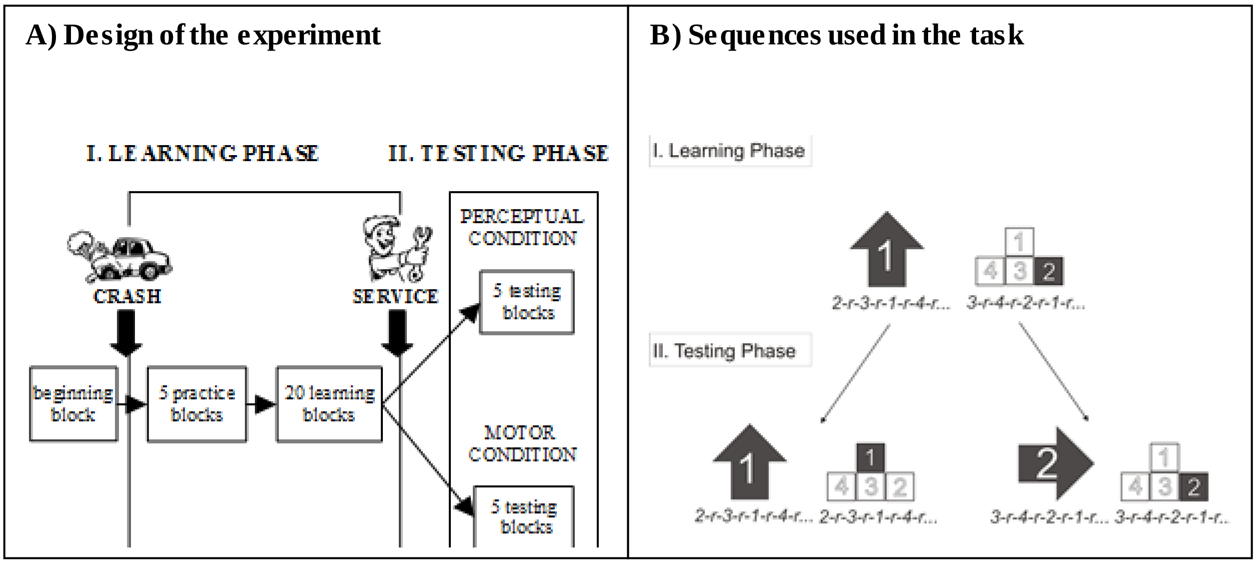

Figure 2.5.1. A) Schematic diagram of the experiment. **B)** In the Perceptual condition, the perceptual sequence was the same and the motor sequence (button presses) changed compared to the sequences in the learning phase. In the Motor condition, key presses followed the learned sequence and the perceptual information changed.

In the learning phase, 5 practice blocks were presented (these were excluded from the analysis), followed by 20 learning blocks with 85 key presses in each block. These 85 key presses included an initial 5 random presses (warm-up; excluded from the analysis), then an eight-element sequence alternated 10 times (2–R–3–R–1–R–4-R, where R represents random trials). The stimulus remained on the screen until the subject pressed the correct button. The next stimulus appeared after a 120 ms delay (response to stimulus interval, RSI) after the subject's correct response (following the parameters of the original task by J. H. Howard Jr. & Howard, 1997). During this delay, a fixation cross was displayed on the screen. Subjects were told to respond as fast and as accurately as they could.

After the learning phase (and a 3 minute long break), the subjects were told that the car had been taken to a service station and the steering wheel had been fixed. They were told to use the answer keys corresponding to the arrows that appeared on the screen (up button for up arrow, left button for left arrow, etc.). In the testing phase, half of the subjects were assigned to the Perceptual condition and the other half to the Motor condition (see Figure 2.5.1A). In the Perceptual condition, subjects responded to the sequence seen during the learning phase (e.g., 2–R–3–R–1–R–4–R, see Figure 2.5.1B), and the appropriate key presses represented a new sequence (also 2–R–3–R–1–R–4–R), which they had not practiced before. In contrast, subjects in the Motor condition had to respond by key presses practiced before (for example 3–R–4–R–2–R–1–R, see Figure 2.5.2) but the corresponding stimuli on the screen followed another sequence (also 3–R–4–R–2–R–1–R), which they had not seen before. Thus, in the Perceptual condition, the perceptual sequence was the same but the motor sequence (key presses) changed compared to the previously practiced sequence. However, in the Motor condition, key presses followed the previously learned sequence and the perceptual information (the sequence of the stimuli displayed on the screen) changed. By comparing the subject's performance between the two conditions, we could determine whether the perceptual and the motor component had the same or different effects on learning. The possible oculomotor aspect of learning was excluded by displaying all the stimuli in the same place (in the center) of the screen.

To explore how much explicit knowledge the subject acquired about the task, we used a short questionnaire after the testing phase. None of the participants reported noticing the sequences in the tasks.

Statistical analysis - We followed the procedures of the original ASRT task (Bennett et al., 2007; Song et al., 2007b) in our analysis because the core structure of the tasks was the same. Given that there was a fixed sequence in the AS-RT–Race task (and in the ASRT task as well), which included alternating random elements (e.g., 2–R–3–R–1–R–4–R), some triplets or runs of three events occurred more frequently than others. For example, in the above illustration, triplets like 2_3, 3_1, 1_4, 4_2 could occur more frequently because the third element could be derived from the sequence or could also be a random element. In contrast, triplets such as 4_1, 4_4 would occur less frequently because in this case, the third element could only be random. In other words, pattern trials were always high frequency, whereas one-fourth of random trials were high frequency by chance. Previous studies have shown that as participants practice, they come to respond more quickly to the high-frequency compared to the low-frequency triplets, thereby revealing sequence-specific learning (triplet type effect; (D. V. Howard et al., 2004; J. H. Howard, Jr. & Howard, 1997; Song, Howard, & Howard, 2007a)). In addition, general motor skill learning was revealed by the overall speed with which participants responded, irrespective of the triplet types. Thus, we obtained measures of both sequence-specific and general motor skill learning in the AS-RT-Race task.

The blocks of the AS-RT-Race task were organized into groups of five to facilitate data processing. A group of five blocks was referred to as an *epoch* (a term given by the ASRT authors). The first epoch contained blocks 1-5, the second epoch contained blocks 6-10, etc. Our analysis focused only on reaction time data because subjects' accuracy remained very high during the entire test (the average was 97% for both conditions in both the learning and testing phases). Median reaction times (RT) were calculated for each subject and in each epoch both for the high and low frequency triplets.

Results

Learning phase – The 2 (TRIPLET: high and low) x 4 (EPOCH: 1-4) Repeated Measures ANOVA with CONDITION (perceptual vs. motor) as the between-subject factor revealed sequence-specific learning (indicated by a significant main effect of the TRIPLET: $F(1,23)=124$, $MSE=56.65$, $p<0.001$, $\eta_p^2=0.63$), as well as general motor skill learning (shown by the significant main effect of the EPOCH: $F(4,20)=8.85$, $MSE=32.53$, $p<0.001$, $\eta_p^2=0.72$), thereby suggesting that the more the subjects practiced, the faster their responses became (see Figure 2.5.2A-B). The two groups (perceptual and motor conditions) did not differ either in sequence-specific or in general motor skill learning (p values>0.31).

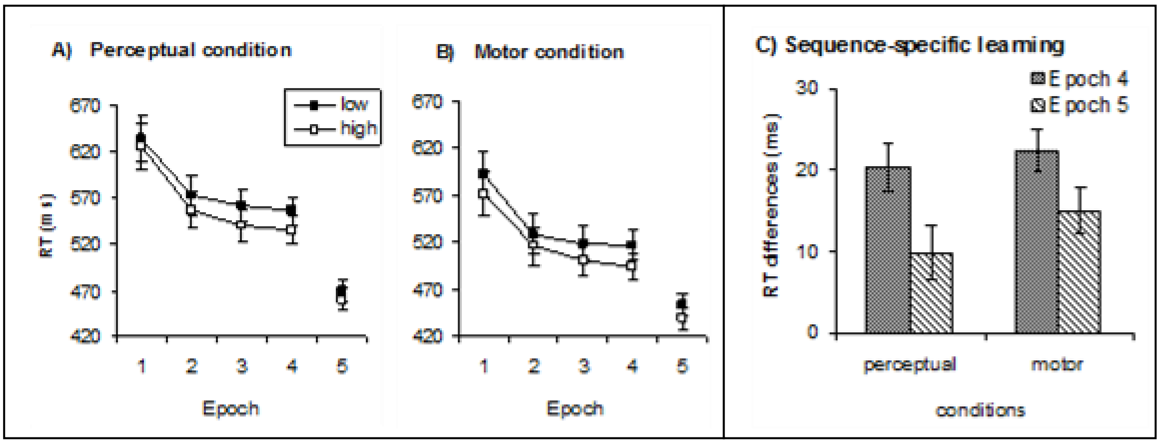

Figure 2.5.2. Results of the Learning Phase (Epoch 1-4) and Testing Phase (Epoch 5) for Perceptual (A) and Motor (B) conditions. Filled squares represent low frequency triplets; open squares represent high frequency triplets. Comparing the sequence-specific knowledge (the RT differences between high and low frequency triplets) of perceptual and motor conditions (C). Error bars indicate standard error of mean (SEM).

Testing phase - To compare the perceptual and motor conditions in the testing phase, a 2 (TRIPLET: high and low) x 2 (EPOCH: 4-5) Repeated Measures ANOVA was conducted with CONDITION (perceptual vs. motor) as the between-subject factor. The main effect of the TRIPLET was significant (F(1,32)=69.72, MSE=139.36, p<0.001, $\eta_p^2=0.69$) such that participants responded faster for high-frequency than for low frequency triplets (see Figure 2.5.2C). The main effect of the EPOCH was also significant (F(1,32)=115.4, MSE=1448.27, p<0.001, $\eta_p^2=0.78$), whereby subjects were faster in the testing phase (455 ms) than in the learning phase (525 ms). Interestingly, the TRIPLET x EPOCH interaction was also significant (F(1,32)=5.75, MSE=117.79, p=0.02, $\eta_p^2=0.15$), thereby suggesting that the sequence-specific knowledge decreased between the learning and the testing phases (the RT difference between the high- and low-frequency triplets was 21 ms in Epoch 4 and 12 ms in Epoch 5). However, despite this decrease, subjects still showed a significant triplet type effect in Epoch 5 (indicated by a one-sample t-test: t(33) =4.52, p<0.001). In addition, there was no difference between the conditions either in sequence-specific (p=0.38) or in general motor skill (p=0.10).

Discussion

Our research investigated the role of perceptual and motor learning in implicit skill learning. We addressed the possibility of demonstrating perceptual transfer beyond motor learning in a testing situation where, after the learning phase, the task continues either with motor sequence or with perceptual sequence while eliminating oculomotor learning. We were able to show learning after the learning phase both in the perceptual and motor conditions. We focused on the perceptual sequence transfer under the former condition, and the motor sequence in the latter. Our results demonstrated that under this research paradigm, both motor and perceptual transfer was significant. These results support the different methods of Song et al. (2008), which demonstrated perceptual learning with probabilistic sequence learning tasks. On the other hand, our results partly differ from that of Willingham et al.(2000), which did not find perceptual learning to be an important element of learning. However, their research design did not eliminate the possibility of oculomotor learning, whereas the present study did. Furthermore, our findings also indicated that there was motor transfer, thereby supporting the results of Willingham et al. (2000) and their implicit motor sequence learning model.

Our findings well complement motor skill learning models (Doyon, Bellec, et al., 2009; Okihide Hikosaka et al., 1999; O. Hikosaka et al., 2002), as well as the neuropsychological and neuroimaging studies that suggest the basal ganglia and the primary and secondary motor cortices play a role in implicit skill learning (Doyon, Bellec, et al., 2009; Grafton, Hazeltine, & Ivry, 1995; Robertson, Press, & Pascual-Leone, 2005; Willingham & Koroshetz, 1993). The task developed in the present study separated motor and perceptual learning, thereby allowing researchers to conduct more detailed studies in cognitive neuroscience for various pathologies affecting implicit skill learning and the underlying mechanisms of motor and perceptual learning.

Conclusion

In our study, we constructed a novel task (AS-RT-Race) to separate the perceptual and motor factors of implicit skill learning. We found that these components underlie the mechanisms behind skill learning to nearly the same extent. Our results draw attention to the fact that skill learning is not a single process. Instead, there are multiple mechanisms in this fundamental learning process. The novel task we developed was demonstrated to be an appropriate method to investigate the components of skill learning in different neuropsychological pathologies (e.g., basal ganglia disorders, Alzheimer’s disease, etc.), and for examining the effects of development, aging and sleep on the motor and perceptual factors contributing to skill learning.

Acknowledgments

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2.6 The effect of secondary task on implicit probabilistic learning[7]

Abstract

During sentence processing we decode the sequential combination of words, phrases or sentences according to previously learned rules. The computational mechanisms and neural correlates of these rules are still much debated. Other key issue is whether sentence processing solely relies on language-specific mechanisms or is it also governed by domain-general principles. In the present study, we investigated the relationship between sentence processing and implicit sequence learning in a dual-task paradigm in which the primary task was a non-linguistic task (Alternating Serial Reaction Time Task for measuring probabilistic implicit sequence learning), while the secondary task were a sentence comprehension task relying on syntactic processing. We used two control conditions: a non-linguistic one (math condition) and a linguistic task (word processing task). Here we show that the sentence processing interfered with the probabilistic implicit sequence learning task, while the other two tasks did not produce a similar effect. Our findings suggest that operations during sentence processing utilize resources underlying non-domain-specific probabilistic procedural learning. Furthermore, it provides a bridge between two competitive frameworks of language processing. It appears that procedural and statistical models of language are not mutually exclusive, particularly for sentence processing. These results show that the implicit procedural system is engaged in sentence processing, but on a mechanism level, language might still be based on statistical computations.

Keywords: sentence processing, statistical learning, implicit/procedural learning, dual task, mental grammar

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[7] Published in Nemeth, D., Janacsek, K., Csifcsak, G., Szvoboda, G., Howard Jr, J. H., & Howard, D. V. (2011). Interference between sentence processing and probabilistic implicit sequence learning. *PLoS One*, *6*(3), e17577.

Introduction

Sentence processing works in a fast, automatic and unconscious way. It is widely accepted that during syntactic processing we decode the sequential and hierarchical combination of words, phrases or sentences according to previously learned and well-established rules. These rules, even if they exist, are represented in the mental grammar, the computational mechanisms and neural correlates of which are still much debated in the literature (McClelland & Patterson, 2002; Pinker & Ullman, 2002). Other key issue in neurolinguistic research is whether sentence processing solely relies on language-specific structures and mechanisms or is it also governed by domain-general computational principles (Christiansen, Kelly, Shillcock, & Greenfield, 2010; Hauser, Chomsky, & Fitch, 2002; Jackendoff & Pinker, 2005). We are trying to build a bridge between frameworks of sentence processing in order to find the 'secret ingredient' of this fundamental human skill.

There are two competing theoretical frameworks regarding the neural underpinnings of language capacities in the human brain. "Dual-system" theories attribute distinct, specialized and innate cognitive and neural components to the mental grammar and the mental lexicon respectively (Chomsky, 1965, 1995; Damasio & Damasio, 1992; Fodor, 1983; Frazier, 1987; Pinker, 1994). According to one such dualistic model, the mental lexicon relies on the declarative memory system, while the mental grammar is subserved by structures involved in procedural memory (Ullman, 2001). The procedural memory system is responsible for gradual, implicit (non-conscious) learning and controlling motor and cognitive 'skills' and 'habits', especially those involving rules or sequences, such as riding a bicycle or using tools and other manipulated objects (Poldrack & Packard, 2003; Squire & Knowlton, 2000; Willingham, 1998). This system is rooted in frontal lobe/basal-ganglia circuits, in particular premotor regions, Broca's area and the caudate nucleus. It also encompasses other structures, including portions of superior temporal cortex and the cerebellum (Ullman, 2001).

In contrast, "single-system" theories posit that words and grammatical rules are learned and utilized by a single non-language-specific system with a broad anatomical distribution (Bates & MacWhinney, 1989; Elman et al., 1996; Rumelhart & McClelland, 1986; Seidenberg, 1997). According to this view, grammatical rules are only descriptive entities; during actual language acquisition we learn the entire statistical structure of the language. Modern connectionist theories argue that learning, representation, and processing of grammatical rules and lexical items are the product of a network, which consists of a large number of simple inter-connected processing units, the connections of which are continuously adjusted on the basis of statistical contingencies in the environment (Elman et al., 1996; Rumelhart & McClelland, 1986; Seidenberg, 1997). In a recent paper, Conway and colleagues (C. Conway, Bauernschmidt, Huang, & Pisoni, 2010) provided evidence that speech perception is related to statistical learning. The statistical learning theory of language has been used to explain mechanisms of constructive grammar (Tomasello, 2003), language development (McMurray, Aslin, & Toscano, 2009; Saffran et al., 1996) and is also supported by studies of artificial language learning (Dienes, Altman, Kwan, & Goode, 1995; Gomez & Gerken, 1999; Misyak, Christiansen, & Tomblin, 2010).

Thus, whereas dual-system theories link syntactic processing primarily to frontal brain regions and procedural memory, single-system theories suggest that grammar appears as the result of general statistical computations within a widespread neural network in the brain. Although implicit/procedural and statistical learning models offer apparently different interpretations for mental processes, a recent theoretical paper highlighted the similarities between the two principles and suggested that they are closely related (Perruchet & Pacton, 2006). The goal of the experiment reported here was to test whether sentence processing relies on general (non-linguistic) statistical computations supporting procedural learning.

During the past decade, new experimental paradigms emerged which successfully address both procedural and statistical motor learning. The Alternating Serial Reaction Time (ASRT) task (J. H. Howard, Jr. & Howard, 1997; Song et al., 2007b) was developed within the context of classical procedural-learning tests, the finger-tapping task and the Serial Reaction Time (SRT) task. Finger-tapping and SRT tasks involve both general skill and sequence-specific learning and they test basal ganglia and cerebellar functions (Doyon, Bellec, et al., 2009; O. Hikosaka et al., 2002; Kincses et al., 2008). The advantage of the ASRT task is that it enables separate parallel assessment of sequence-specific and general skill learning. In the classical SRT task, the structure of a sequence is deterministic with the stimuli following a simple cyclically repeating pattern (e.g. 213412134121341213412…, where numbers refer to distinct events within the repeating 21341 pattern). In contrast, repeating events alternate with random elements in the ASRT task. This means that the location of every second stimulus on the screen is determined randomly. If, for instance, the sequence is 1234, where the numbers represent locations on the screen, in the ASRT task the sequence of stimuli will be 1R2R3R4R, with ‘R’ representing a random element. Because fixed, sequence-specific and random stimuli are alternating, some sequences of three events (called ‘triplets’) occur more frequently than others. For example, in the above illustration 1x2, 2x3, 3x4 and 4x1 would occur often, whereas 1x3 or 4x2 would occur infrequently. Following previous studies, we refer to the former as *high-frequency* triplets and the latter as *low-frequency* triplets (Nemeth, Janacsek, Londe, et al., 2010; Song et al., 2007b) . In a typical ASRT task, participants are instructed to respond to different stimulus events (e.g., the same image appearing in one of four possible locations on the screen) by pressing different response keys (e.g., a separate letter on a keyboard assigned to each of the four image locations) as fast and accurately as they can. Earlier results have shown that as people practice the ASRT task, they respond more quickly to the high- than low-frequency triplets revealing probabilistic, sequence-specific learning (J. H. Howard, Jr. & Howard, 1997; Song et al., 2007b). This learning is statistical in nature, because it depends on the frequency of the event sequences. In addition, the process is entirely implicit, as participants do not recognize the alternating structure of the sequences even after extended practice or when sensitive recognition tests are used to assess explicit knowledge (J. H. Howard, Jr. & Howard, 1997; Song et al., 2007b).

In the present study, we investigated the relationship between sentence processing and implicit sequence learning in a dual-task paradigm in which one task was a non-linguistic task (ASRT for measuring probabilistic implicit sequence learning), while others were a sentence comprehension task relying on syntactic processing and two control conditions. The majority of previous works on the relationship between language functions and the declarative/procedural system were based on manipulating regular and irregular forms of words (Ullman, 2001). Given that these tasks are not sensitive to other linguistic rules, such as word order, embedded structures etc., we used the comprehension of complex sentences, which we considered a more sensitive marker of grammatical processing. We selected two control conditions: a non-linguistic one (math condition) and a linguistic task (word processing task) where grammatical computations were not required, only the utilization of the mental lexicon. Since the ASRT task relies both on the procedural system and on statistical computations, we hypothesized that implicit sequence-specific learning would be attenuated by simultaneous sentence comprehension if the two tasks engage the same neurocognitive system(s). Finding interference would serve as direct evidence that operations for sentence processing depend on statistical computations of non-linguistic nature.

Methods

Ethics Statement

Ethics approval was obtained by Psychology Ethics Committee at University of Szeged, Institute of Psychology. All subjects provided signed informed consent agreements and received no financial compensation for their participation.

Participants

Twenty-six students between 21 and 25 years (average age: 22.54, SD: 1.17; 4 male/22 female) from the University of Szeged participated in the study. Subjects did not suffer from any developmental, psychiatric or neurological disorders.

Procedure

A dual-task paradigm (A. Baddeley, Della Sala, Papagno, & Spinnler, 1997; D'Esposito et al., 1995; Foerde et al., 2006; Poldrack et al., 2005) was designed during which our subjects were instructed to perform the ASRT and a parallel task simultaneously (DT condition). Three types of parallel tasks were used: (1) sentence comprehension, (2) word recognition and (3) mathematical addition. Investigating the interference between sentence comprehension and procedural learning was the primary goal of the study, whereas the other two parallel tasks served as linguistic (word recognition) and non-linguistic (mathematical addition) control tasks. While both the sentence comprehension and word recognition tasks require access to the mental lexicon, mental grammar is only utilized by sentence comprehension. We used a within subject design with every subject performing all three parallel tasks, but with a different order. The subjects had a 5-10 minute-long rest between the different sessions. During these breaks, we collected demographic data (age, years of education, etc.). In order to objectively compare the degree of implicit learning in the three dual task sessions, we inserted three single task (ST) probe blocks (blocks 1, 8 and 15) during which the ASRT was the only task to perform (Figure 2.6.1).

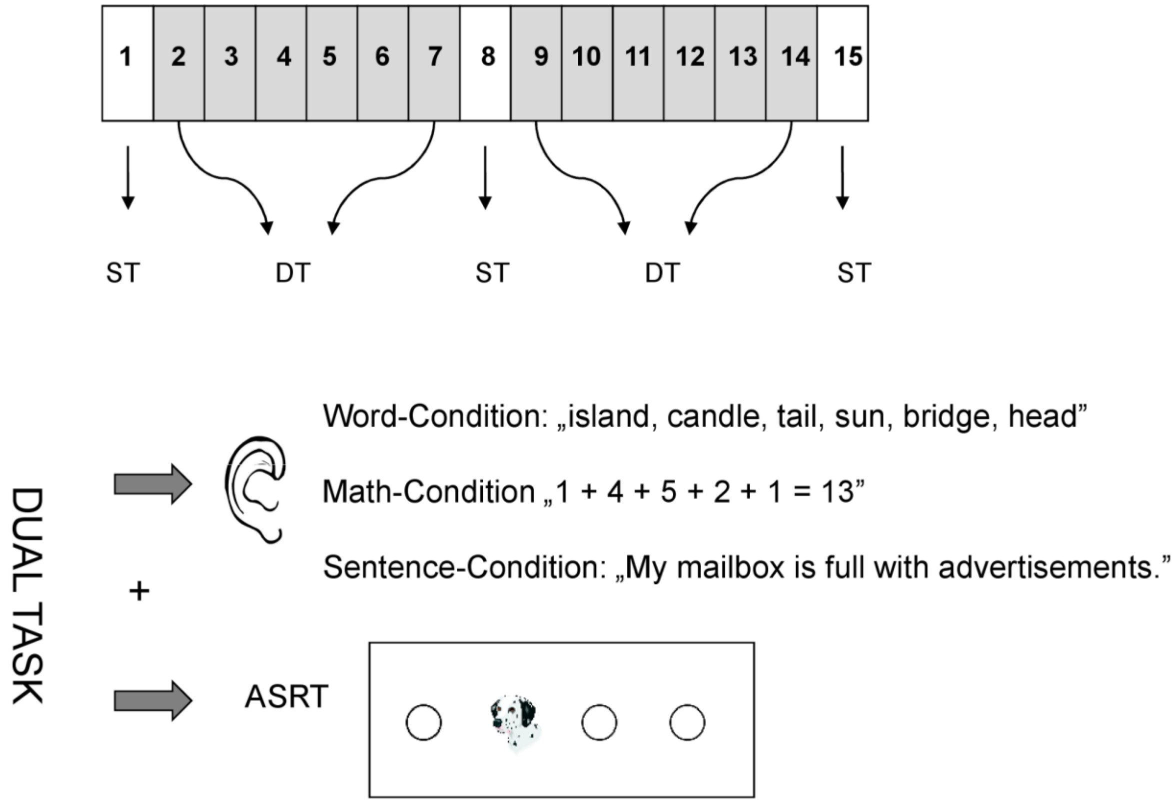

Figure 2.6.1: Schematic design of the experiment. The presentation order of the conditions was counterbalanced between subjects. In the ASRT task blocks 1, 8 and 15 were single task (ST) blocks without parallel task, whereas in other blocks (2-7; 9-14) our subjects had to perform one of the three parallel tasks as well (DT condition)

Tasks

Alternating Serial Reaction Time (ASRT) Task

We used a modification of the original ASRT task (Nemeth, Janacsek, Londe, et al., 2010) in which a visual stimulus (a dog's head) appeared in one of the four empty circles on the screen and subjects had to press a key that corresponded to the actual spatial location (see Figure 2.6.1).

E-prime 1.2 was used for stimulus presentation and data collection. The computer was equipped with a special keyboard with four heightened keys (Y, C, B and M in the standard Hungarian IBM PC keyboard; the letter Y corresponds to the letter Z on standard English keyboards), each corresponding to one of the circles in left to right order. Before beginning the experiment, detailed instructions appeared on the screen. We emphasized that the aim was to try to respond as quickly and as correctly as possible.

The ASRT consisted of 15 blocks, with 85 key presses in each block: the first five stimuli were random events for practice purposes, after which an eight-element alternating sequence (e.g. 1R2R3R4R) repeated ten times. In order to objectively assess the degree of sequence-specific and general skill learning during the sessions, we inserted three probe blocks (blocks 1, 8 and 15), where no parallel task was present. Following Howard and Howard (1997), stimuli were presented 120 ms after the previous motor response. As one block took about 1.5 minutes, each session with different DT conditions lasted approximately 30-35 minutes. Between stimulus blocks, the participants received feedback on the screen about their overall reaction time and accuracy. They could then rest for maximum 20 seconds before starting a new block.

For each subject, three different ASRT sequences (A: 1r3r2r4r; B: 4r3r1r2r; C:2r3r4r1r) were used for every session, and the occurrence of the different sequences was balanced across subjects and parallel tasks as well. Consequently, every sequence was used in all three DT conditions, but for different subjects.

To explore how much explicit knowledge subjects acquired about the sequence learning task, we administered a short questionnaire (Song et al., 2007b) after the experimental session. This questionnaire included specific questions such as “Have you noticed anything special regarding the task?” or “Have you noticed some regularity in the sequence of stimuli?”. The experimenter rated subjects’ answers on a 5-item scale, where 1 corresponded to “Nothing noticed” and 5 to “Total awareness”. None of the subjects reported noticing the sequence in the ASRT task.

Parallel tasks

Every parallel task was presented in the auditory modality during the execution of the ASRT task in such a way that the parallel task items were read out loud by the experimenters and the subjects had to give a yes/no answer to each one. Participants were told to answer aloud as fast and accurately as possible after the actual task (word list, addition or sentence) was presented. The experimenter registered the answers and monitored continuously if participants followed the instructions.

Sentence processing (Sentence condition) - The subjects were instructed to listen to sentences and to decide after each one whether they were correct or not. Five to nine sentences were presented per ASRT block. Every sentence contained 6 words with half of the sentences being incorrect containing one of the following three error types: semantic, pragmatic or syntactic. Although we chose an error detection task to keep our subjects’ attention focused on the task, the main emphasis was on overall sentence processing and not on error detection *per se*.

Word recognition (Word condition) - In the word processing condition the subject had to recognize words in lists containing 6 items. In order to control attention, the subjects had to decide if the list contained a non-word item that occurred at each position within a list with equal probability. Five to nine word lists were presented per ASRT block. Half of the lists contained a non-word, half of them did not.

Mathematical addition (Math condition) - The subject were presented with an addition of five items and the possible result (e.g. 4+9+2+1+3=19) after which they had to decide whether the result was correct or not. Similarly to the other two conditions, five to nine additions were presented per ASRT block. Half of the additions were correct, half were not.

Each list contained 6 items (words in the sentence comprehension or word recognition tasks and numbers in the math condition) in order to avoid varying working memory loads. In addition, we asked all subjects to name the most difficult parallel task at the end of the experiment.

Statistical analysis

Both sequence-specific and general skill learning were evaluated by parameters obtained in the single task probe blocks of the ASRT. Sequence-specific learning was calculated by comparing RTs obtained for high- and low-frequency triplets, whereas general skill learning was determined by comparing RTs between the three probe blocks, regardless of triplet frequency. As expected (Nemeth, Janacsek, Londe, et al., 2010), participants' accuracy was very high in the probe blocks (mean value > 97% for all groups), so we focused on reaction time (RT) analysis. All significant results are reported together with the Greenhouse-Geisser ε correction factors, where applicable.

Results

RT data were entered into a repeated-measures ANOVA, with TRIPLETS (high vs. low frequency), PROBE BLOCKS (blocks 1, 8 and 15) and CONDITIONS (sentence, word and math) as within-subject factors. The main question of the study was answered by the presence or absence of interaction between the CONDITION factor and one or both of general and sequence-specific skill learning.

Repeated-measures ANOVA revealed sequence-specific learning (indicated by a significant main effect of TRIPLET: $F(1,25)=11.59$, $MSE=224.21$, $p=0.002$, $\eta_p^2=0.32$), and general skill learning as well (indicated by a significant main effect of PROBE BLOCK: $F(2,24)=14.87$, $MSE=639.95$, $p<0.001$, $\eta_p^2=0.55$). The CONDITION x TRIPLET interaction was also significant ($F(2,24)=3.56$, $MSE=190.01$, $p=0.044$, $\eta_p^2=0.23$), suggesting that sequence-specific learning differed between the three dual task conditions (see Figure 2.6.2A). General skill learning was not affected by the dual task conditions (CONDITION x BLOCK interaction: $F(4,100)=1.61$, $MSE=1035.65$, $p=0.18$, $\eta_p^2=0.06$). Other interactions regarding the probe block data were not significant, nor was the main effect of CONDITION, suggesting that the overall RTs did not differ across conditions. Subsequent ANOVAs conducted separately for all dual task conditions revealed significant sequence-specific learning in both the word and math conditions (main effect of TRIPLET: $F(1,25)=13.85$, $MSE=158.66$, $p=0.001$, $\eta_p^2=0.36$; $F(1,25)=5.86$, $MSE=247.67$, $p=0.02$, $\eta_p^2=0.19$, respectively), whereas it was not significant in the sentence condition ($F(1,25)=0.06$, $MSE=197.90$, $p=0.82$, $\eta_p^2=0.002$).

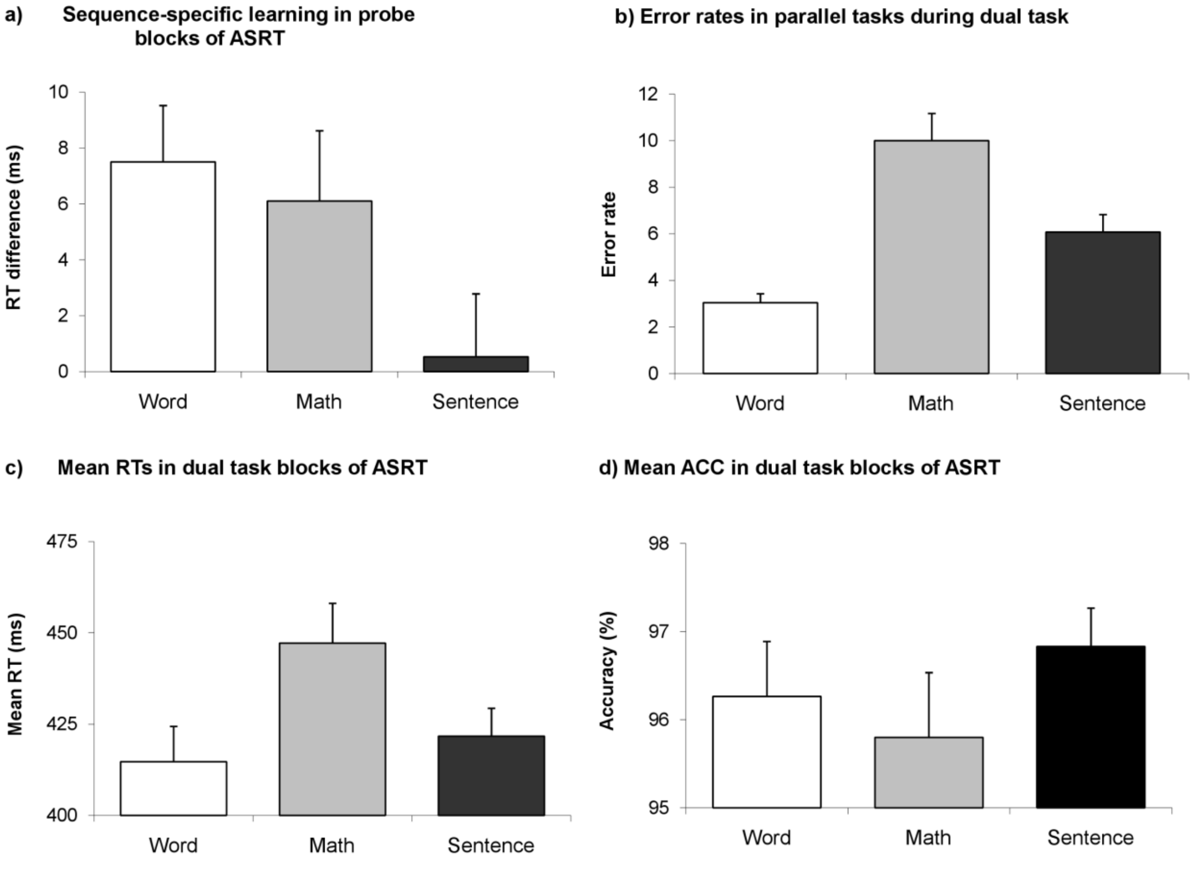

Figure 2.6.2: A) Mean RTs of sequence-specific learning (difference between high and low frequency triplets) in probe blocks of the ASRT task for all dual task conditions. There was significant sequence-specific learning in the Word and Math condition, but no learning in the Sentence condition. B) Error rates in parallel task during dual task. There were significantly more errors in the Math condition than in the other two conditions. C) Mean RTs in dual task blocks of the ASRT for all dual task conditions. The Math condition was the most difficult: the RTs differed significantly from the Word and Sentence conditions, while the latter two did not differ significantly from each other. D) Mean accuracy (ACC) in dual task blocks of the ASRT for all dual task conditions. The Math condition was the most difficult: participants were less accurate in the Math condition than in the Sentence

condition, while the Word-Math and Word-Sentence conditions did not differ significantly from each other. Error bars indicate standard errors of the mean (SEM).

Error rates of the parallel task (Figure 2.6.2B) measured during the dual task conditions were significantly higher in the math condition (Mean: 10, SD=5.95) than in the sentence comprehension (Mean=6.08, SD=3.84; p=0.001) and word processing condition (Mean=3.04, SD=1.99; p<0.001), and word and sentence conditions differed from each other as well (p=0.01). Mean overall RTs during the dual task blocks of the ASRT (Figure 2.6.2C) were significantly longer in the math condition (Mean=447.22, SD=55.54) than in the sentence comprehension (Mean=421.71, SD=39; p=0.01) and word processing tasks (Mean=414.71, SD=49.41; p=0.03), while we found no differences between the sentence and word conditions (p=0.34). Moreover, mean accuracy during the dual task blocks of the ASRT (Figure 2.6.2D) was significantly lower in the math condition (Mean=95.8, SD=4.05) than in the sentence condition (Mean=96.8, SD=2.45; p=0.04), while we found no differences between sentence-word (p=0.35), and word-math conditions (p=0.14). Finally, subjects' reports unanimously confirmed that the math condition was the most difficult. These results indicate that the modulation of sequence-specific learning was primarily affected by the nature of the parallel task and its underlying neural structures, and not by the difficulty of the parallel task itself.

Discussion

In our study we found both general skill and sequence specific learning across tasks, however, we also found a clear dissociation - the sentence processing task diminished probabilistic implicit sequence learning, while the other two tasks did not produce a similar effect. This interference was not due to the complexity or relative difficulty of the parallel tasks, because (1) error rates of the parallel tasks were significantly higher in the math condition than for the linguistic tasks, (2) participants were significantly slower and less accurate in this math condition and (3) subjective reports confirmed that the math task was the most difficult.

The ASRT task is classically considered as an implicit motor learning task that depends on the procedural memory system (Song et al., 2007b). The interference between the ASRT task and sentence processing but not word recognition partly supports the declarative/procedural model of language functions, according to which the mental grammar but not the lexicon engages the procedural system (Sahin, Pinker, Cash, Schomer, & Halgren, 2009; Ullman, 2001). The most important aspect of this study however, is that it goes beyond the classification of sentence processing as a procedural process. Sequence-specific learning in the ASRT task is based on unconscious detection of the conditional probabilities within the stimulus sequence as reflected in the high- and low-frequency triplets (Howard Jr, Howard, Dennis, & Kelly, 2008).

Several theories emphasized the highly probabilistic nature of language, which might indeed be linked to domain-general processes, such as statistical learning (Christiansen et al., 2010; Misyak et al., 2010; Saffran et al., 1996). Artificial language learning is perhaps the most popular paradigm in this field, but to our knowledge, this is the first study demonstrating a link between language processing and a clearly non-linguistic probabilistic learning task (i.e. the ASRT task). Since the ASRT task shares features with both procedural and statistical learning, its interference with sentence processing might explain why syntactic processing has been previously associated with both types of learning. However more investigations with more language control conditions are needed to find out exactly which aspect of sentence processing interferes with probabilistic sequence learning.

Another interesting aspect of our results is that implicit sequence learning in the ASRT task is related to the motor system (Doyon, Bellec, et al., 2009; O. Hikosaka et al., 2002; Kincses et al., 2008), which supports the motor theory of language (M. H. Fischer & Zwaan, 2008) and might contribute to the evolutionary interpretations of language development (Jackendoff & Pinker, 2005).

In summary, we found that operations for sentence processing utilize resources underlying non-domain-specific probabilistic procedural learning in the human brain. Our study provides a bridge between two competitive frameworks of language processing. It appears that procedural/statistical models of language processing are not mutually exclusive, particularly for sentence processing. The implicit procedural system is crucial for sentence processing, but on a mechanism level, language might still be based on statistical computations.

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Thanks to my host professor: Michael T. Ullman, Georgetown University, Washington DC.

2.7 The role of working memory in implicit probabilistic learning[8]

Abstract

The relationship between implicit/incidental sequence learning and working memory motivated a series of research because it is plausible that higher working memory capacity opens a “larger window” to a sequence, allowing thereby the sequence learning process to be easier. Although the majority of studies found no relationship between implicit sequence learning and working memory capacity, in the past few years several studies have tried to demonstrate the shared or partly shared brain networks underlying these two systems. In order to help the interpretation of these and future results, in this mini-review we suggest the following factors to be taken into consideration before testing the relationship between sequence learning and working memory: 1) the explicitness of the sequence; 2) the method of measuring working memory capacity; 3) online and offline stages of sequence learning; and 4) general skill- and sequence-specific learning.

Keywords: skill learning, sequence learning, implicit vs. explicit learning, working memory, dorsolateral prefrontal cortex

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Although implicit sequence learning is a subconscious process which is believed to be independent from general cognitive resources such as working memory, in the past few years several studies have set out to demonstrate the shared or partly shared brain networks underlying these two systems. For example, disrupting the dorsolateral prefrontal cortex (DLPFC), a structure involved in working memory, with transcranial magnetic stimulation (TMS) impairs implicit sequence learning (Pascual-Leone, Wassermann, Grafman, & Hallett, 1996; Robertson et al., 2001). However, the role of PFC in implicit sequence learning is controversial: while some studies found activation of the DLPFC in implicit sequence learning (Pascual-Leone et al., 1996; Robertson et al., 2001; Schwarb & Schumacher, 2009), others failed to find such a relationship (Bo, Peltier, Noll, & Seidler, 2011; P. C. Fletcher et al., 2005; A. Rieckmann et al., 2010). Moreover, several studies showed that manipulations reducing the dominance of the PFC and/or the medial temporal lobe (MTL), such as a demanding secondary task (Foerde et al., 2006), a distractor task inserted between the learning sessions (Brown and Robertson, 2007), hypnosis during learning (Nemeth, Janacsek, Polner, and Kovacs, 2012) or neuropharmacological blockage (Frank, O'Reilly, and Curran, 2006), had no effect or even led to performance improvements in sequence learning tasks. These latter findings support the competitive nature of the PFC- and MTL-dependent and basal ganglia-dependent memory systems (Poldrack et al., 2001).

To refine the interpretation of these and future results, we outline several factors in this mini-review to be taken into consideration before planning brain imaging, psychophysiology, and behavioral studies on the relationship between sequence learning and working memory.

Evidence for independence between implicit sequence learning and working memory

The relationship between implicit sequence learning and working memory motivated a series of research because it is plausible to suggest that higher working memory capacity opens a “larger window” to a sequence, allowing thereby the sequence learning process to be easier (Frensch and Miner, 1994; Howard and Howard, 1997). However, the majority of studies (see Table 2.7.1) found no relationship between implicit sequence learning and working memory capacity. For instance, Feldman et al. (1995) demonstrated that there is no significant correlation between sequence learning scores (performance on a random block minus performance on a sequence block) on a 10-element deterministic implicit serial reaction time (SRT) task and span tasks (Digit and Backward Digit Span Tasks; and Wisconsin Card Sorting Test). Unsworth and Engle (2005) found that high and low working memory capacity individuals (measured by Operation Span Task) did not differ in performance on implicit sequence learning; moreover, the implicit sequence learning was independent from general fluid intelligence. Kaufman et al. (2010) found similar results using a probabilistic implicit sequence learning task and demonstrated with structural equation modeling that working memory is independent from implicit learning. Frensch and Miner (1994) also failed to find a significant correlation between implicit/incidental sequence learning in the single-task condition and performance on span tasks. Bo et al. (2011; Bo et al., 2012) did not find a correlation between classical learning score on the SRT task and working memory measures either.

Neuropsychological investigations also suggest the independence of implicit sequence learning and working memory. For example, a recent study found working memory deficits, but intact implicit sequence learning abilities in individuals with Obstructive Sleep Apnea (Nemeth, Csábi, Janacsek, Varszegi, & Mari, 2012). In addition, several studies showed intact implicit sequence learning in groups with intellectual disabilities, for example in Autistic Spectrum Disorder (Barnes et al., 2008; J. Brown, Aczel, Jimenez, Kaufman, & Grant, 2010; Nemeth, Janacsek, Balogh, et al., 2010) or Down-Syndrome (Vicari, Vicari, Verucci, & Carlesimo, 2007). As working memory is highly correlated with general intellectual abilities while implicit learning is independent of IQ, (e.g., Kaufman et al., 2010), we can interpret these results as indirect evidence for independence between implicit sequence learning and working memory. In sum, despite partly overlapping brain networks (Pascual-Leone et al., 1996; Sefcsik et al., 2009), these two systems seem to be separate from each other on the functional level.

Factors influencing effects of working memory on sequence learning

Explicitness of the sequence - If the sequence learning is explicit/intentional, working memory differences emerge in the sequence learning tasks (Unsworth & Engle, 2005). Frensch and Miner (1994, Experiment 1), as well as Bo and colleagues (Bo, Borza, & Seidler, 2009; Bo et al., 2012), found significant correlation between working memory and some measures of explicit sequence learning. These studies suggest that working memory is engaged in explicit learning to guide the focus of attention and cognitive control (Nelson Cowan, 1998; Jimenez, 2003; Kaufman et al., 2010). This idea is also supported by the more attention demanding dual-task experiments (Frensch and Miner, 1994, Experiment 2) in which sequence learning performance under dual-task conditions correlated with Digit Span and Location Span Tasks. In line with this argument, functional magnetic resonance imaging (fMRI) and positron emission tomography (PET) studies of sequence learning found greater activity in prefrontal cortical areas during explicit sequence learning compared to the implicit condition (Destrebecqz et al., 2005; P. C. Fletcher et al., 2005; Honda et al., 1998). Prefrontal cortical areas are thought to be engaged in working memory performance as well (Champod & Petrides, 2010; Smith & Jonides, 1999).

Measures of working memory – As the above mentioned studies have shown, different methods could lead to different working memory effects on sequence learning. Performance on short-term and working memory *span tasks* (e.g., Forward and Backward Digit Span, Operation Span, Reading Span, and Listening Span Tasks) shows no correlation with implicit/incidental sequence learning, while *dual-task* methods (Frensch and Miner, 1994) and *change detection working memory tasks* (Bo et al., 2011) can demonstrate working memory effects on implicit sequence learning. In contrast, most studies have found working memory effects on explicit sequence learning using any type of WM measure (e.g., Unswoth and Engle, 2005; Bo et al., 2009; Weitz et al., 2011). In addition, we also have to consider the difference between verbal and visuospatial working memory depending on whether verbal (e.g., letters, digits, words) or visuospatial material (e.g., shapes, colors, locations) needs to be remembered. These two types of working memory can relate to sequence learning in different ways, suggesting some extent of domain-specificity. One can assume that the performance in a sequence learning task, where the sequence is defined as a stimulus-series of different locations (e.g., classical SRT task, Nissen and Bullemer, 1987), might correlate stronger with visuospatial than with verbal working memory capacity. For example, in the study of French and Miner (1994, Experiment 1), visuospatial sequence learning correlated with Location Span but not with Digit Span. Similarly, Bo et al. (2009) found a relationship between sequence learning, measured by the chunk length of a visuospatial sequence learned by the participants, and visuospatial working memory capacity. In contrast, verbal working memory might play a greater role in sequence learning of verbal material (e.g. Dennis et al., 2006; Weitz, O'Shea, Zook, & Needham, 2011). For example, a recent study by Weitz et al. (2011) showed correlation between the learning of a verbal sequence (Hebb digits task) and verbal working memory capacity. Note, however, that all of these latter findings regarding domain-specificity were related to explicit and not to implicit sequence learning.

Stages of sequence learning - The differentiation between *online* and *offline phases of learning* also needs to be considered, as significant changes in the acquisition do not occur only during practice (online periods) but also between practice (offline) periods. The process that occurs during the offline periods is referred to as consolidation, which means stabilization of a memory trace after the initial acquisition; it can result in increased resistance to interference or even improvement in performance following an offline period (Krakauer & Shadmehr, 2006;

Nemeth, Janacsek, Londe, et al., 2010; Robertson, 2009; Song, 2009). The previously discussed studies measured sequence learning by one learning session without an offline period and barely showed working memory's effect on sequence learning. On the other hand, if we administer multiple learning sessions with, for example, 24-hour delay periods, we are able to examine the effect of consolidation processes on the relationship between sequence learning and working memory capacity. For example, Howard and Howard (1997) as well as Schwartz et al. (2003) administered more learning sessions distributed throughout several days and found significant working memory effects on a sequence learning task. However, they did not analyze the effect of consolidation specifically (the performance from all learning sessions were collapsed). Future studies need to test the relationship between sequence knowledge after a consolidation period and working memory capacity.

General skill vs. sequence-specific learning – There seem to be a number of misunderstandings regarding the sequence learning indices used in the studies focusing on the association between sequence learning and working memory. Recent studies highlight that at least two aspects of learning have to be differentiated in the sequence learning experiments. The RT performance improvement as a result of practice can be attributed both to general familiarization with the task (termed as *general skill learning*, or *general practice effects*) and to learning the sequential structure/regularity of the task specifically (termed as *sequence-specific learning*) (Janacsek and Nemeth, 2012; Song, Howard, and Howard, 2007). In the classical SRT task (Nissen & Bullemer, 1987), the more the participants practice, the faster they are on blocks containing the repeated sequential structure. When this sequence is changed to a random series of stimuli at the end of practice, participants' response rate becomes slower. In this task, sequence learning can be measured in different ways: 1) by the reaction time (RT) decrease in sequential blocks (i.e., participants are generally faster in the last sequence block compared to the first sequence block; e.g., Bo, Jennett, et al., 2011); 2) by the RT difference between the last sequence block and the subsequent random block. The latter measure is more widely accepted in sequence learning literature (e.g., Keele et al., 2003; Robertson, 2007) for critical view see (Reed & Johnson, 1994). For example, using these indices, Bo et al. (2011) found a positive correlation between working memory capacity and the rate of RT decrease (thus, the RT change in sequential blocks), but not between working memory and RT difference in the last sequence and the following random block (which is supposed to reflect sequence-specific learning better). In a more recent study, Bo, Jennett and Seidler (2012) replicated these results in elderly participants. One potential concern regarding these results is whether it is possible to separate the above mentioned general skill and sequence-specific learning components in the classical SRT task. Namely, the RT decrease in the sequential blocks can reflect both general skill and sequence-specific learning. The contribution of these two factors to performance improvement cannot be precisely determined. As Bo et al. (2011, 2012) found correlation only with the RT decrease in sequence blocks, not with the sequence/random difference score, we can suggest that working memory might be more related to general skill learning than to the sequence-specific learning. Therefore, further studies and different analysis methods are needed to clarify the relationship between working memory and general skill learning or sequence-specific learning. For example, as Verwey (1996) proposed, participants respond to individual sequence elements one by one at the beginning of the sequence learning, but consecutive elements can be formed into a single representation ("chunk") once the sequence is learned. Thus, it is possible to determine the mean chunk length in the SRT task with higher length (larger window into the sequence structure) reflecting better sequence-specific learning. Using this analysis method, Bo et al. (2009) found a relationship between working memory capacity and mean chunk length in *explicit* sequence learning. This raises the question of whether such a relationship is present between the mean chunk length in *implicit* sequence learning and working memory.

Another possible approach for future studies can be the use of *probabilistic* sequences instead of deterministic ones (as in the SRT task), since probabilistic second- or higher-order sequence regularities give us the opportunity to analyze sequence-specific and general skill learning separately and more precisely. For example, in the alternating SRT (Howard and Howard, 1997) task, repeating stimuli alternate with random ones, thus every second element in the stream is determined randomly. Hence, it is possible to *track sequence-specific learning continuously* by comparing responses to the random and sequence elements in all blocks. This could help to investigate the relationship between sequence-specific learning and working memory more precisely.

Neurocognitive background of the relationship between working memory and sequence learning

A growing body of evidence suggests that the fronto-striatal circuit, including the caudate nucleus and lateral PFC, plays a critical role in working memory performance. In this circuit, PFC is thought to be responsible for the coordination of encoding, maintenance, and manipulation of information, by, for example, biasing the processing in posterior sensory-and multimodal association areas (Bar, 2003; Desimone & Duncan, 1995; Miller & Cohen, 2001;

Nobre, 2001). The striatum, on the other hand, modulates the working memory performance by increasing or decreasing the inhibition of the PFC (Ashby et al., 2010). Recent studies highlight that the striatum is primarily involved in the manipulation processes, for example filtering out the irrelevant information (McNab & Klingberg, 2007), conflict monitoring (Beste et al., 2012), and sequencing (Riley, Moore, Cramer, & Lin, 2011).

In this fronto-striatal circuit, the last two decades of implicit sequence learning research showed the involvement of striatum in the acquisition of sequence knowledge (Keele et al., 2003; Rieckmann et al., 2010), while the role of PFC remained inconclusive. Determining the specific conditions where working memory capacity and sequence learning correlate can help us to unravel the complex role of PFC in cognition and specifically in sequence learning. In most studies finding correlation between these two measures, participants were aware of the sequence and had the intention to improve their performance utilizing this sequence knowledge. In these cases a higher extent of PFC-dependent coordination and cognitive control is implemented to perform the task. Supporting this argument, fMRI studies found greater PFC activation in this explicit/intentional version of sequence learning compared to the implicit/incidental one (e.g., Fletcher et al., 2005). Thus, the relationship between working memory capacity and sequence learning in these cases might be based on the mutual PFC-dependent coordination component of the performance.

However, in some cases implicit sequence learning was also correlated with working memory capacity. In most of these studies working memory capacity was measured by a complex task where the manipulation of the information, not only the maintenance, was relevant for a high task performance. Based on these results we can suggest that this observed correlation is primarily attributable to the greater involvement of the striatum in these working memory tasks. The recent studies showing the specific role of striatum in information manipulation are in line with this assumption (Beste et al., 2012; Riley et al., 2011). The other plausible explanation could be that most of the studies finding a relationship administered more sessions to measure sequence learning (Howard & Howard, 1997; Schwartz et al., 2003), allowing a better consolidation of the acquired information. One might assume that processes engaged in this offline phase of sequence learning share more similarity with working memory than the online sequence processing (e.g., maintaining the acquired information in an active state for a longer period can help stabilize the memory traces). However, these studies did not contrast the online and offline performance directly and did not involve brain imaging; therefore future research needs to clarify this issue.

Summary

In our review, we briefly touched on some relevant issues regarding the possible relationship between implicit sequence learning and working memory: 1) the explicitness of the sequence; 2) measures of working memory capacity; 3) online and offline stages of sequence learning; and 4) general skill- and sequence-specific learning. With these factors we can better interpret the results of studies on the relationship between sequence learning and working memory. However, note that because of the length limitation of the mini-review we could not critically investigate the question of whether the implicit sequence learning and working memory tasks discussed in this mini-review are the most adequate measures for tapping the constructs they were designed to tap (Kane, Conway, Miura, & Colflesh, 2007; Moisello et al., 2009; Unsworth & Engle, 2006).

Based on the studies included in this mini-review (Table 2.7.1), we suggest a relationship between working memory and 1) explicit rather than implicit sequence learning, 2) potentially to a higher extent with general skill learning than with sequence-specific learning, 3) with some specificity to verbal or visuospatial domains (i.e., higher correlation between visuospatial working memory and learning of visuospatial sequences than learning verbal ones). In the reviewed literature only two studies have administered multiple sessions to measure sequence learning. However, they analyzed the relationship between working memory and sequence learning by collapsing the online and offline components. Therefore, the effect of consolidation on this relationship remains an open question needing to be addressed in further research. In addition, future studies also would benefit from taking into account which measures are used for determining the working memory capacity (i.e., span or change detection tasks) as well as sequence learning (i.e., general RT improvements, RT difference between sequence and random elements, chunk length of the sequence, etc.).

Considering the factors discussed in this mini-review will aid in the design of future experiments, in the interpretation of results, and a deeper appreciation of the relationship between sequence learning and working memory and underlying brain structures.

Table 2.7.1. Studies investigating the relationship between sequence learning and working memory (WM). "Mixed" indicates when general skill and sequence-specific learning cannot be separated in the analysis method that the study used.

Study	Explicit /Implicit	WM measure	Online /offline	General skill /sequence-specific	WM effect
Frensch and Miner (1994), Exp. 1	Explicit	Span task	Online	Sequence-specific	Yes
	Implicit				No
Frensch and Miner (1994), Exp. 2	Implicit	Span task, dual task condition	Online	Sequence-specific	Yes
Feldman et al. (1995)	Implicit	Span task	Online	Sequence-specific	No
Howard and Howard (1997)	Implicit	Span task	Online (Session 1)	Sequence-specific	Not analyzed separately
			Online + Offline (Session 1-6)		Yes
Schwartz et al. (2003)	Implicit	Span task	Online (Session 1)	Sequence-specific	No
			Online + Offline (Session 1-6)		Yes
Unsworth and Engle (2005)	Explicit	Span task	Online	Sequence-specific	Yes
				Mixed	Yes
	Implicit	Span task	Online	Sequence-specific	No
				Mixed	No
Bo et al. (2009)	Explicit	Change detection	Online	Sequence-specific	Yes
Kaufman et al. (2010)	Implicit	Span task	Online	Sequence-specific	No
Bo et al. (2011)	Implicit	Span task	Online	Mixed	No
				Sequence-specific	No
		Change detection		Mixed	Yes

				Sequence-specific	No
Weitz et al. (2011)	Explicit	Span task	Online	Sequence-specific	Yes
	Implicit				No
Bo et al. (2012)	Explicit	Change detection	Online	Sequence-specific	No
				Mixed	Yes

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2.8 Implicit learning in Autism[9]

Abstract

Background: Although autistic people have shown impairments in various learning and memory tasks, recent studies have reported mixed findings concerning implicit learning in ASD. Implicit skill learning, with its unconscious and statistical properties, underlies not only motor but also cognitive and social skills, and it therefore plays an important role from infancy to old age.

Methodology/Principal findings: We investigated probabilistic implicit sequence learning and its consolidation in Autism Spectrum Disorder (ASD). Three groups of children participated: thirteen with high-functioning ASD, 14 age-matched controls, and 13 IQ-matched controls. All were tested on the Alternating Serial Reaction Time Task (ASRT), making it possible to separate general skill learning from sequence-specific learning. The ASRT task was repeated after 16 hours. We found that control and ASD children showed similar sequence-specific and general skill learning in the learning phase. Consolidation of skill learning and sequence-specific learning were also intact in the ASD compared to the control groups.

Conclusions/Significance: These results suggest that autistic children can use the effects/results of implicit learning not only for a short period, but also for a longer stretch of time. Using these findings, therapists can design more effective educational and rehabilitation programs.

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[9] Published in Nemeth, D., Janacsek, K., Balogh, V., Londe, Z., Mingesz, R., Fazekas, M., ... & Vetro, A. (2010). Learning in autism: implicitly superb. *PloS one*, *5*(7), e11731.

Introduction

Implicit learning is defined as the acquisition of information or motor skill without conscious access to what was learned or even to the fact that learning occurred (Perruchet & Pacton, 2006; Reber, 1967). Autism Spectrum Disorder (ASD) is characterized by social, communicative and motor impairments (APA, 1994). The semantic and episodic memories of people with autism have often been studied, but neurocognitive studies of procedural learning and implicit cognition have received less attention. The extent of learning abilities of ASD individuals is debated (Dawson, Mottron, & Gernsbacher, 2008). In the present study, we examined implicit motor skill learning in ASD to probe the functional integrity of this type of fundamental learning mechanism.

Most models of motor skill learning (Doyon, Bellec, et al., 2009; Okihide Hikosaka et al., 1999; O. Hikosaka et al., 2002; Kincses et al., 2008; Robertson, 2009) emphasize the role of the basal ganglia and the cerebellum, while the role of the hippocampus in this process remains inconclusive (Albouy et al., 2008; Schendan et al., 2003). Neuropsychological studies have shown that sequence learning is impaired in people with Huntington's and Parkinson's diseases (Willingham, 1997), demonstrating the impact of striatal dysfunction on this type of perceptual-motor learning. Functional brain imaging studies also show the involvement of the cerebellum, striatum and motor cortices in implicit sequence learning tasks including the Serial Reaction Time (SRT) and the Alternating Serial Reaction Time (ASRT) tasks (Fletcher et al., 2005; Rauch et al., 1997; Willingham, Salidis, & Gabrieli, 2002). In addition, Muller et al. (2004) reported that autistic individuals showed abnormal fMRI activity patterns in premotor cortex as well as greater individual variability in the activation maps.

Previous studies showed mixed results regarding implicit sequence learning of autistic people. Mostofsky and colleagues (Mostofsky, Goldberg, Landa, & Denckla, 2000) found impaired sequence learning when testing autistic children. They used the SRT task, developed by Nissen and Bullemer (1987), in which participants were instructed to respond as quickly and as accurately as possible to the location of a stimulus that was presented at one of four possible locations on the monitor in a series of trials. Unknown to the participants, the locations of stimuli follow a predefined sequence, and participants typically become faster at responding to the locations predicted by the sequence compared to random trials. Mostofsky et al. (2000) tested a 10-trial fixed sequence repeated 8 times in a block, across a total of 5 blocks using a longer 1500 ms interval, instead of the customary 120-300 ms response-to-stimulus interval used in SRT tasks (eg. J. H. Howard, Jr. & Howard, 1997; M. J. Nissen & Bullemer, 1987). Gordon and Stark (2007) tested sequence learning in autistic participants in two tasks, one with an 8-element, and the other a 4-element fixed sequence. Their results revealed marginal learning with the 8-element fixed sequence task and significant learning with the 4-element task. As in Mostofsky et al. (2000), this study used an unusually long response to stimulus interval (RSI) of 500 ms.

Four issues arise with the two studies above: 1) With a fixed-sequence series the possibility of an explicit strategy arises, because it is easier to become aware of the sequence, since the same sequence is presented repeatedly. 2) Both in the 10- and 8-element sequences the frequency of the elements was not balanced. Some elements could have occurred more frequently than others, which could increase the possibility of pattern recognition of the sequence, making the learning process explicit rather than implicit. In addition, it is possible that the learning observed was due at least partly to learning the relative frequencies of individual events rather than of sequences of events. 3) The long RSI values in the above studies could also contribute to developing an explicit strategy. Research has suggested that the longer the RSI, the more probable that explicit strategies are used (Destrebecqz & Cleeremans, 2001; Destrebecqz & Cleeremans, 2003; Jimenez, Mendez, & Cleeremans, 1996). 4) In the various neuropsychological and neurodevelopmental disorders in which IQ is involved, it has been found that explicit learning is correlated with IQ, while implicit learning is relatively independent of IQ level (J. Brown et al., 2010; Gebauer & Mackintosh, 2007; Reber, Walkenfeld, & Hernstadt, 1991). Explicit processes, therefore, suffer more under circumstances with IQ impairment. If learning relies on explicit strategies, then autistic individuals could be learning less than controls due to impairments in explicit rather than implicit learning.

Barnes and colleagues (2008) overcame the above limitations by using a 3-element version of the ASRT task (J. H. Howard, Jr. & Howard, 1997), which is a modified version of the SRT task. In classical SRT tasks the structure of a sequence is deterministic with the stimuli following a simple repeating pattern as in the series 213412431423, where numbers refer to distinct events. In contrast, in the ASRT task (J. H. Howard, Jr. & Howard, 1997; Remillard, 2008) repeating events alternate with random elements. This means that the location of every second stimulus on the screen is determined randomly. If, for instance, the sequence is 123, where the numbers represent locations on the screen, in ASRT the sequence of stimuli will be 1R2R3R1R2R3R…, with R representing a random element. The sequence is thus better hidden than in the classical SRT task and it is also possible to track sequence-specific learning continuously by comparing responses to the random and sequence elements within each testing block. This structure is called a probabilistic second-order (lag-2) dependency (J. H. Howard, Jr. & Howard, 1997; Remillard, 2008), because to predict element ’n’ we need to know element n-2. Barnes et al. (2008) used a 120ms RSI, and they found intact learning in Autism compared to a control group matched for age and IQ. The authors suggest that the fronto-striatal-cerebellar functions are spared in autism.

It is possible that Barnes et al. (2008) found intact implicit learning because participants were mostly children with Asperger's syndrome, who have better cognitive abilities than children with simple autism. It is also possible that this group found intact implicit learning because they used the ASRT with 3 elements (i.e., 3 possible locations corresponding to 3 possible responses), which could be too easy to detect deficits. However, in a recent study Brown et al. (2010) also observed intact implicit sequence learning in a probabilistic SRT task introduced by Schvaneveldt & Gomez (1998). In this task the RSI was 0 ms to reduce the possibility of creating an explicit strategy (Brown et al., 2010; Destrebecqz & Cleeremans, 2001; Destrebecqz & Cleeremans, 2003).

To our knowledge, consolidation of implicit or procedural learning has not been studied in autism, although some research has investigated consolidation of episodic and semantic long-term memories (Ben Shalom, 2003; Minshew & Goldstein, 2001; Toichi & Kamio, 2003). Because some aspects of these domains show impairments in autism, it is important to investigate the implicit consolidation processes as well. When examining consolidation it is essential to know that skill learning occurs not only during practice in the so-called *online* period, but also between-practice during the so- called *offline* phase. The process that occurs during the offline period is referred to as consolidation, which means stabilization of a memory trace after the initial acquisition or even improvement in performance following an offline period (Krakauer & Shadmehr, 2006). Such consolidation is important in considering the long-term acquisition of skills; even if implicit learning is intact, it is possible that autistic individuals are impaired in consolidation, thus forgetting the skills over the longer term. This might explain the apparent contradiction of intact implicit learning in autistic people even though they are known to be weaker in communicative and social skills (APA, 1994).

In our study we used the ASRT task to investigate implicit learning and consolidation in autism. The ASRT task allows separation of general skill learning and sequence specific learning during both online and offline periods. General skill learning is reflected in the overall reaction time, whereas sequence-specific learning is reflected in the difference between the reaction time to predictable, sequence events as opposed to less predictable random ones. We also examined the effect of a 16-hour delay on learning performance, to test whether consolidation is intact. The present study goes beyond previous studies (Barnes et al., 2008; J. Brown et al., 2010; Gordon & Stark, 2007; Mostofsky et al., 2000) in two ways: 1) we used a more difficult 4-element ASRT task with 4 possible locations and 4 corresponding responses, instead of the 3-element version used by Barnes et al. (2008), and 2) we investigated the consolidation of implicit learning over a 16-hour period.

Materials and methods

Participants

Thirteen children with ASD, 13 IQ-matched, and 14 age-matched children participated in the experiment. Their characteristics are described in Table 2.8.1. The IQ-matched control group differed significantly from the other two groups in mean age (IQ control and ASD: t(24)=2.25; p=0.034; IQ and AGE control: t(25)=-2.05, p=0.51), whereas the mean IQ in the AGE-matched control group was significantly higher than in the ASD (t(25)=-2.12, p=0.044) and IQ-matched control group (t(25)=-2.12, p=0.044).

The children's IQ was measured by the Wechsler Intelligence Scale for Children (WISC, 3rd ed.). All children with ASD were diagnosed using the criteria in the DSM-IV (APA, 1994), and had received clinical evaluations both according to the Autism Diagnostic Interview (ADI) and the Autism Diagnostic Observation Schedule (ADOS) (Lord et al., 2000; Lord, Rutter, & Le Couteur, 1994). The mean score of the ADOS was 3.00 (SD=1.58) for Communication and 5.67 (SD=1.87) for Reciprocal Social Interaction domains. The mean score of ADI-R was 10.75 (SD=4.65) for Reciprocal Social Interaction, 11.25 (SD=6.15) for Communication and 4.87 (SD=1.25) for Repetitive Behavior domains. Four of the ASD group members had a diagnosis of Asperger's syndrome. Children with neurological or psychiatric disorders, or IQ of less than 70 were excluded from the experiment. Control groups did not suffer from any developmental, psychiatric or neurological disorders, and did not have sleeping disorders. Parents reported that all children had 7-8 hours of sleep a day. 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 Psychology Ethics Committee at University of Szeged, Institute of Psychology.

Table 2.8.1. General data of participants

	Age		IQ		Sex	ASRT learning
	Mean (SD)	Range	Mean (SD)	Range		
ASD (n=13)	11.77 (3.14)	7-17	93.15 (20.67)	70-146	11 M / 2 F	10/13
IQ-matched control (n=13)	9.23* (2.59)	8-17	96.54 (17.65)	74-139	13 M	12/13
AGE-matched control (n=14)	11.57 (3.27)	7-17	109.07* (12.83)	90-138	12 M / 2 F	12/14

Procedure

There were two sessions in the experiment (see Figure 2.8.1): a learning phase (Session 1) and a testing phase (Session 2) separated by a 16-hour interval (±2 hours). The first session was in the afternoon (between 2 – 4 PM), and took approximately 30-35 minutes; the second session was in the morning (between 7 – 9 AM) and lasted 5-10 minutes.

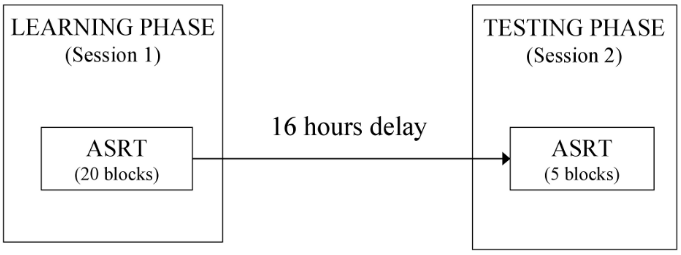

Figure 2.8.1. Experiment design.

Alternating Serial Reaction Time (ASRT) Task

We used a modified version of the original ASRT task (J. H. Howard, Jr. & Howard, 1997), in which a stimulus (a dog’s head) appeared in one of the four empty circles on the screen and the subject had to press a corresponding key (Y, C, B and M on Hungarian keyboard) when it occurred (Nemeth, Janacsek, Londe, et al., 2010).

Session 1 (the learning phase) consisted of 20 blocks of the ASRT, with 85 key presses in each block - the first five trials were random (for practice and to make it more difficult to discover the pattern explicitly), then the 8-element sequence (i.e., 4 pattern events alternating with 4 randomly determined ones) repeated 10 times. Following Howard et al. (1997) each stimulus was presented 120 ms following the previous response (response-to-stimulus interval, RSI). Between blocks, the subjects received feedback about their overall reaction time and accuracy, and then they were given a 10 - 20 second rest before starting a new block. Session 2 (the testing phase) consisted of 5 blocks of the ASRT, because we only focused on offline changes of previously acquired knowledge (as presented by Nemeth, Janacsek, Londe, et al., 2010; Song et al., 2007b). The number of key presses per block and the RSI were the same as Session 1.

There are 6 possible sequences in which each of the four positions occurs once and only once (i.e., 1r2r3r4r, 1r2r4r3r, 1r3r4r2r, 1r3r2r4r, 1r4r2r3r, 1r4r3r2r), and each of these was used approximately equally often across subjects within a group, but the sequence for a given subject was identical during Session 1 and Session 2.

To explore how much explicit knowledge subjects acquired about the task, we administered a short questionnaire (similar to Song et al., 2007b) after the second session. 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 the stimuli?" The experimenter rated subjects' answers on a 1-5 scale, where 1 was "Nothing noticed" and 5 represented "Total awareness." None of the subjects reported noticing the sequence either in the ASD, the IQ- or AGE-matched control groups.

Statistical analysis

As there is a fixed sequence in the ASRT with random elements inserted (e.g. 1 R 2 R 3 R 4 R, when R represents random trials) some triplets or runs of three events occur more frequently than others. For example, for the above example sequence 1x2, 2x3, 3x4, and 4x1 would occur often whereas 1x3 or 4x2 would occur infrequently. Following previous studies, we refer to the former as high-frequency triplets and the latter as low-frequency triplets. Pattern trials are always high-frequency, whereas one-fourth of the random trials are high-frequency by chance. Thus, high-frequency triplets occur 62.5% of the time and low-frequency triplets occur 25% of the time (excluding repetitions, e.g. 333, and trills, e.g. 313). As is typical, we have excluded repetitions and trills from analyses because they usually reveal preexisting response biases and because they are always low frequency for all subjects and hence (unlike the remaining triplets) are not counterbalanced (D. V. Howard et al., 2004). Earlier results 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 (D. V. Howard et al., 2004; J. H. Howard, Jr. & Howard, 1997; Song et al., 2007b), and participants remain unaware of such learning. In addition, general motor skill learning is revealed in the ASRT task with a decrease in average response speed, irrespective of the triplet types. Thus, we are able to obtain measures of both sequence-specific and general motor skill learning in the ASRT task.

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 blocks 6-10, etc. (Barnes et al., 2008; Song et al., 2007b). The analyses were performed as in Song et al's (2007b) and Nemeth et al. (2010) We report both the reaction times (RT) and accuracy data; however, our focus is primarily on RT. For RT we calculated means for correct responses only (eliminating trills and repetitions and RTs that fell more than 3 standard deviations from the mean RT for that subject), separately for trials ending high versus low frequency triplets and for each subject and each epoch. For accuracy, we used the mean percentages of the correct responses.

Results

Online learning during session 1

Reaction time

To investigate learning during Session 1 (learning phase) a mixed design ANOVA was conducted on the first 4 epochs of the RT data shown in Figure 2.8.2A-C, with (TRIPLET: high vs. low) and (EPOCH: 1-4) as within-subjects factors, and GROUP (ASD, IQ- and Age-matched control groups) as a between-subjects factor. Thus, sequence-specific learning would be revealed by main effects and/or interactions with TRIPLET.

There was significant sequence-specific learning (indicated by the significant main effect of TRIPLET: F(1,37)=37.55, MSE=747.57, p<0.000001, $\eta_p^2=0.50$) such that RT was faster on the high than low frequency triplets. There was also general motor skill learning (shown by the significant main effect of EPOCH: F(3,111)=14.27, MSE=15368.84, p<0.000001, $\eta_p^2=0.28$), such that RT decreased across epochs. There were no group differences in learning (no interactions with group were significant; all p's > 0.40). The only significant effect regarding Group was the main effect (F(2,37)=4.58, MSE=256569.47, p=0.02, $\eta_p^2=0.20$), reflecting that the Age-matched control group responded faster than both the ASD and IQ-matched control groups (p's <0.04). The ANOVA conducted on transformed data (using the same method as Barnes et al, 2008: low minus high differences in epochs / RT of low frequency triplets) revealed the same results.

Subsequent TRIPLET x EPOCH ANOVAs on the RTs, conducted separately for each group confirmed that each group showed both general skill learning and sequence-specific learning. For the ASD group there was a significant main effect of TRIPLET, F(1,12)=22.21, MSE=683.68, $p=0.001$, $\eta_p^2=0.65$ and the main effect of EPOCH was $F(3,36)=2.14$, MSE=28145.74, $p=0.11$, $\eta_p^2=0.15$. The EPOCH x TRIPLET interaction was not significant, $F(3,36)=0.15$, MSE=987.34, $p=0.93$, $\eta_p^2=0.05$. For the IQ-matched control group there were significant main effects of TRIPLET, $F(1,12)=7.29$, MSE=1166.34, $p=0.02$, $\eta_p^2=0.38$ and of EPOCH, $F(3,36)=8.40$, MSE=9873.67, $p<0.0001$, $\eta_p^2=0.41$. The TRIPLET x EPOCH interaction was not significant ($F(3,36)=0.53$, MSE=815.31, $p=0.67$, $\eta_p^2=0.04$). For the Age-matched control group the main effects of TRIPLET and EPOCH were also significant ($F(1,13)=13.03$, MSE=420.00, $p=0.003$, $\eta_p^2=0.44$; $F(3,39)=10.37$, MSE=8647.24, $p<0.0001$, $\eta_p^2=0.50$; respectively). The TRIPLET x EPOCH interaction did not reach significance ($F(3,39)=2.21$, $p=0.10$, $\eta_p^2=0.15$).

Accuracy

The same analyses were conducted on accuracy measures. The ANOVA revealed significant sequence-specific learning (indicated by the significant main effect of TRIPLET: $F(1,37)=17.35$, MSE=0.001, $p<0.0001$, $\eta_p^2=0.32$), such that the accuracy was greater on high than low frequency triplets. The main effect of EPOCH was also significant ($F(3,111)=3.13$, MSE=0.002, $p=0.029$, $\eta_p^2=0.08$), such that accuracy decreased across epochs (which reflects falling accuracy for low frequency triplets). There were no group differences in learning (no interactions with group were significant; all p values > 0.61). The main effect of Group was not significant ($F(2,37)=1.14$, MSE=0.015, $p=0.33$, $\eta_p^2=0.06$), reflecting that all groups responded with similar accuracy rates (ASD group 94 %, IQ-matched control 92 %, Age-matched control 94 %).

Subsequent TRIPLET x EPOCH ANOVAs were conducted separately for each group to confirm the results. For the ASD group there was a significant main effect of TRIPLET, ($F(1,12)=5.37$, MSE=0.001, $p=0.039$, $\eta_p^2=0.31$), whereras of the main effect of EPOCH did not reach significance ($F(3,36)=2.21$, MSE=0.002, $p=0.10$, $\eta_p^2=0.15$). For the IQ-matched control group there was only a marginally significant main effect of TRIPLET, ($F(1,12)=4.05$, MSE=0.001, $p=0.067$, $\eta_p^2=0.25$), whereas the main effect of EPOCH was not significant, ($F(3,36)=0.48$, MSE=0.004, $p=0.70$, $\eta_p^2=0.04$). For the AGE-matched control group the main effect of TRIPLET was significant ($F(1,13)=8.36$, MSE=0.001, $p=0.013$, $\eta_p^2=0.39$), and the main effect of EPOCH was marginally significant ($F(3,39)=2.83$, MSE=0.001, $p=0.051$, $\eta_p^2=0.18$). The TRIPLET x EPOCH interaction was not significant in any group (all p's > 0.36).

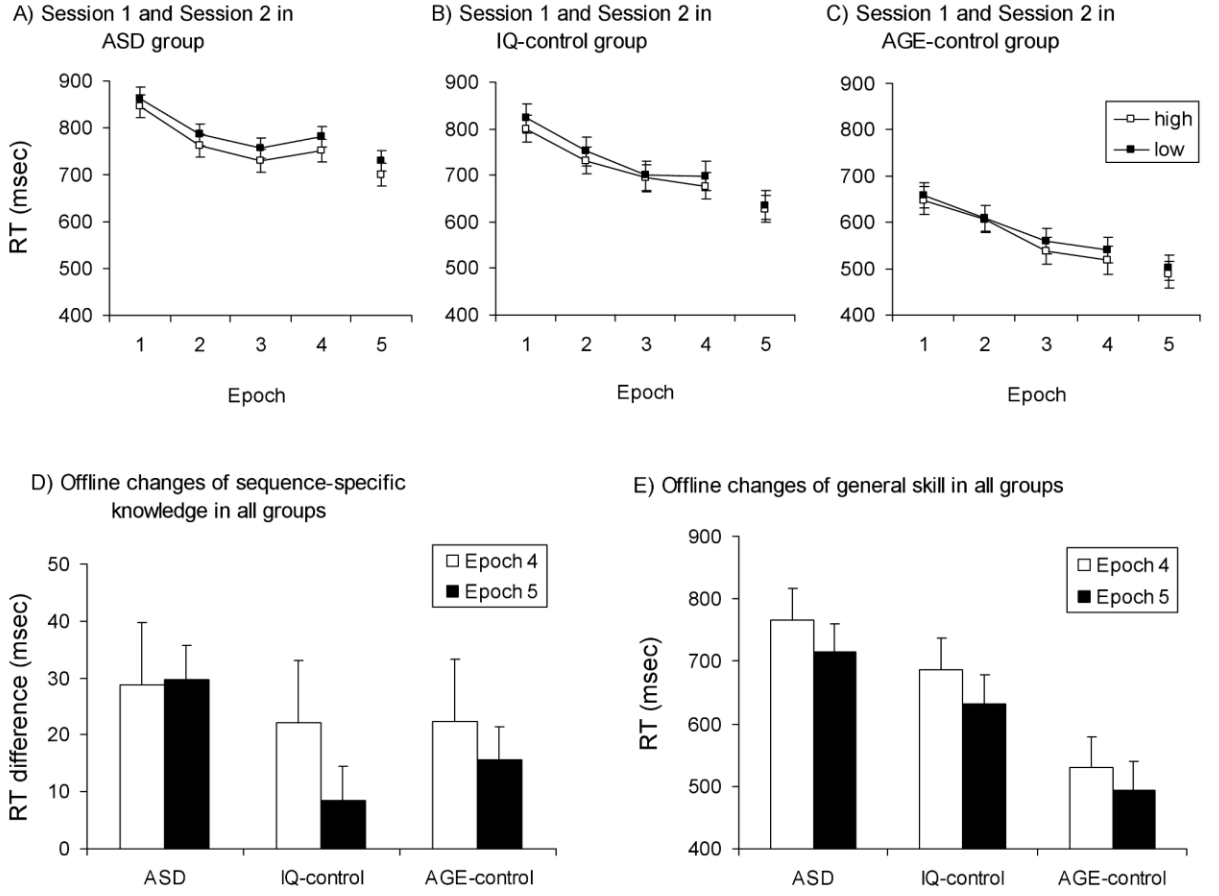

Figure 2.8.2. Results of the experiment. RTs of Session 1 (epoch 1-4) and Session 2 (epoch 5) for ASD (A), IQ-matched (B) and AGE-mathed (C) control groups. The RT differences between the high (open squares) and low frequency (filled squares) triplets indicate sequence-specific learning, whereas the decrease of reaction time (regardless of triplet type) indicates general skill learning. In Session 1 all groups showed significant sequence-specific and general skill learning. D) Offline changes of sequence-specific knowledge for all groups. The sequence learning effect (SLE) is the RT on low frequency minus RT on high frequency trials; this effect on the last epoch of Session 1 (Epoch 4) does not differ significantly from that of the first epoch of Session 2 (Epoch 5). E) Offline changes of general skill for all groups; there was no difference in overall RT between Epoch 4 and 5 for any group. Error bars indicate SEM.

Offline changes of sequence-specific knowledge

To define the index for offline sequence-specific learning, we calculated the Sequence Learning Effect (SLE) which is the RT/accuracy difference for the low versus high frequency triplets for the last epoch of Session 1 (Epoch 4). This index shows the magnitude of sequence-specific learning at the end of the first session (Barnes et al., 2008). Similarly, we calculated this Sequence Learning Effect for the first epoch of Session 2 (Epoch 5). These SLE scores (shown in Figure 2.8.2D) were submitted to a mixed design ANOVA with EPOCH (Epoch 4 and 5) as a within-subjects factor and GROUP (ASD, IQ- and Age-matched control groups) as a between-subjects factor. Thus, any offline changes in sequence-specific learning would be revealed by main effects and/or interactions with EPOCH. In the ANOVA on RT difference scores, neither the main effect of EPOCH, nor the EPOCH x GROUP interaction reached significance (F(1,37)=0.72, MSE=1157.37, p=0.40, η_p^2=0.02; F(2,37)=0.30, MSE=1157.37, p=0.74, η_p^2=0.02; respectively). The subsequent paired t-tests conducted separately for each group confirmed these results (all p's > 0.20). Thus, there was no evidence of offline changes (improvement or deterioration) of sequence-specific knowledge regardless of group.

In the same analysis conducted on the accuracy Sequence Learning Effects (Accuracy on High Frequency minus that on Low Frequency) neither the main effect of EPOCH (F(1,37)=0.13, MSE=0.001, p=0.72, η_p^2=0.004), nor the EPOCH x GROUP interaction was significant (F(2,37)=2.24, MSE=0.001, p=0.12, η_p^2=0.11).

Offline changes of general skills

To examine offline general skill learning we calculated the overall RT/accuracy (combined across triplet types) for the last epoch of Session 1 and the first epoch of Session 2; the greater the RT decrease from Session 1 to Session 2, the larger the offline general skill improvement was. Further, a lack of increase in RT between the two sessions (with a 16-hour time delay between sessions) would signal that the participant's retention of general skill was intact. These overall RTs were used in a mixed design ANOVA with EPOCH (Epoch 4 and 5) as a within-subjects factor and GROUP (ASD, IQ- and Age-matched control groups) as a between subject factor. The ANOVA revealed offline improvement of general skill (shown in Figure 2.8.2E) in that the main effect of EPOCH was significant, (F(1,37)=15.06, MSE=3012.21, p<0.001, η_p^2=0.29), reflecting the faster overall RTs for the first epoch in Session 2 compared to those at the end of Session 1. The EPOCH x GROUP interaction was not significant, F(2,37)=0.28, MSE=3012.21, p=0.76, η_p^2=0.015.

This evidence for offline consolidation of general skill relies on comparing RT on epoch 5 to that on epoch 4, so it is possible that the faster RT on epoch 5 is simply due to learning that occurred during epoch 5 (Nemeth, Janacsek, Londe, et al., 2010). To rule out this possibility, we conducted the same analysis for Epoch 3 and 4 (within Session 1). Neither the main effect of EPOCH, nor the EPOCH x GROUP interaction was significant (F(1,37)=0.01, MSE=7287.32, $p=0.97$, $\eta_p^2<0.001$; $F(2,37)=0.47$, MSE=7287.32, $p=0.63$, $\eta_p^{2=}0.025$). This suggests that the offline effects we observed were not simply due to continued learning.

The results of accuracy analysis also confirmed these findings. When comparing the Epoch 4 and Epoch 5 (across sessions), ANOVA revealed a significant main effect of EPOCH ($F(1,37)=13.82$, MSE=0.001, $p=0.001$, $\eta_p^2=0.27$), reflecting an offline increase in overall accuracy (from 92.5 % to 95.4 %). There was no significant difference among the groups (EPOCH x GROUP interaction: $F(2,37)=1.13$, MSE=0.001, $p=0.33$, $\eta_p^2=0.06$). The ANOVA conducted for Epoch 3 and 4 (within Session 1) revealed a trend for a main effect of EPOCH ($F(1,37)=3.01$, MSE=0.001, $p=0.09$, $\eta_p^2=0.075$), but with a reverse pattern: they were less accurate in the Epoch 4 compared to the Epoch 3 (93.5 % versus 92.5 %). The EPOCH x GROUP interaction was not significant ($F(2,37)=0.92$, MSE=0.001, $p=0.41$, $\eta_p^2=0.05$).

Discussion

Our goal was to investigate whether implicit sequence learning and consolidation are impaired in children with ASD. We used a task that allowed us to differentiate between general skill and sequence-specific learning. We found that ASD children showed general skill learning and implicit learning of probabilistic sequences similar to that of two groups of controls, one matched in IQ and the other in age. In addition, the groups did not differ in consolidation; over a 16-hour period between sessions, we observed no forgetting of sequence-specific learning, as well as offline improvements in general skill, with no significant differences among groups. We believe our study to be the first to investigate implicit learning consolidation in autism.

The findings of the online learning (Session 1) are similar to those of Barnes et al. (2008) and Brown et al. (2010), who also found probabilistic implicit learning to be intact in samples of autistic children. Our results build on these earlier studies in that we show intact learning of a more difficult regularity, in that we used a 4-element ASRT task, instead of the 3-element version in Barnes et al. (2008). Nonetheless, accepting the null hypothesis requires caution. Small sample size and great variability in responses could reduce our ability to detect group differences in learning, however, previous studies with similar findings and similar sample sizes support our conclusions.

Why has the current study and several others found intact implicit sequence learning in this population (e.g. Barnes et al., 2008; Brown et al., 2010) while others did not (e.g. Mostofsky et al., 2000)? Brown et al. (2010) has suggested that explicit strategies could affect the differences in these findings: they reason that such strategies could help in learning deterministic sequences (but not probabilistic ones, since they are more difficult to discover explicitly). This research group also argues that high RSI values could contribute to strategy building: Gordon & Stark (2007) and Mostofsky et al. (2000) used 500-1500 ms whereas Barnes et al. (2008) and Brown et al. (2010) used 120 and 0 ms, respectively. Higher RSIs can lead to more explicit strategies and learning (Destrebecqz & Cleeremans, 2003). Thus, according to Brown's hypothesis performance is influenced by the use of explicit strategies (J. Brown et al., 2010). Using explicit strategies/explicit processes is highly correlated with IQ levels, whereas implicit processes are not (J. Brown et al., 2010; Gebauer & Mackintosh, 2007; Reber et al., 1991). Brown et al. (2010) also reason that ASD individuals are prone to solving tasks explicitly, as shown in several studies (e.g., Theory of Mind performance is mediated explicitly in ASD (Happé, 1995; Hill, Berthoz, & Frith, 2004)). Thus, their impairments may be reflecting impaired explicit, not implicit learning. When there is no chance to use explicit strategies, as in our study, or in Barnes' (2008) and Brown's (2010) the autistic participants are able to reveal their intact implicit learning.

A different hypothesis explaining the contradictory research results can be drawn from Happé & Frith (2006) who suggest that ASDs have attentional preference for local over the global context. It is possible that longer RSIs make it even more difficult for ASD participants to engage in global-context processing because the increased time between events makes it difficult to group them. Thus, longer RSIs would put ASD participants at a disadvantage in sequence learning compared to controls. Testing these hypotheses will require more research.

The results of the present study concerning consolidation are similar to those of Song et al. (2007b) and Nemeth et al. (2010). Like the healthy young and older adults in these earlier studies, our ASD and control groups remembered the sequence between sessions as shown by a lack of decline in Sequence Learning Effect over the 16 hours between sessions. In addition, as had been the case for the adults in these earlier studies, all three groups of children showed offline enhancement of general skill in that they started their second session at a faster response rate than the end of the first session. However, neither study (Nemeth, Janacsek, Londe, et al., 2010; Song et al., 2007b) found a sleep effect in the general skill learning or in the sequence-specific learning. This is important because ASD has been highly associated with sleep difficulties (APA, 1994). Thus, whether consolidation is intact or defective in autism it is most likely not the result of sleep disturbance. The fact that our ASD children did not show deficits in consolidation, is also consistent with evidence suggesting that sleep may not play a critical role in consolidation of implicit sequence learning (Nemeth, Janacsek, Londe, et al., 2010; Robertson, Pascual-Leone, & Press, 2004; Song, 2009; Song et al., 2007b).

Moreover, our findings draw attention to the fact that children acquire the hidden sequences very fast, as they are sensitive to statistical probabilities already in the first epoch of learning. This early sensitivity may reflect greater neural plasticity and is less typical among adults (D. V. Howard et al., 2004; Nemeth, Janacsek, Londe, et al., 2010; Song et al., 2007b).

In summary, this study found that implicit sequence-specific and general skill learning are unimpaired in participants with ASD, and that consolidation of the learning is intact as well. This suggests that autistic children can use the effects/results of implicit learning not only for a short period, but also for a longer stretch of time. Learning seems to get embedded into the cognitive system, which could play an important role in therapy. Learning in general relies on implicit and explicit processes at the same time. If implicit sequence learning is spared relative to explicit learning in ASD (Dawson et al., 2008), then emphasizing implicit processes could improve real-life learning in ASD. Using these results, therapists can design more effective educational and rehabilitation programs. Our findings suggest that learning mechanisms associated with frontal-striatal-cerebellar anatomy are partly intact in ASD.

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2.9 Implicit probabilistic learning in Mild Cognitive Impairment[10]

Abstract

Mild Cognitive Impairment (MCI) causes slight but noticeable disruption in cognitive systems, primarily executive and memory functions. However, it is not clear if the development of sequence learning is affected by an impaired cognitive system and, if so, how. The goal of our study was to investigate the development of probabilistic sequence learning, from the initial acquisition to consolidation, in MCI and healthy elderly control groups. We used the Alternating Serial Reaction Time task (ASRT) to measure probabilistic sequence learning. Individuals with MCI showed weaker learning performance than the healthy elderly group. However, using the reaction times only from the second half of each learning block – after the reactivation phase - we found intact learning in MCI. Based on the assumption that the first part of each learning block is related to reactivation/recall processes, we suggest that these processes are affected in MCI. The 24-hour offline period showed no effect on sequence-specific learning in either group but did on general skill learning: the healthy elderly group showed offline improvement in general reaction times while individuals with MCI did not. Our findings deepen our understanding regarding the underlying mechanisms and time course of sequence acquisition and consolidation.

Keywords: Mild Cognitive Impairment, offline learning, statistical learning, implicit learning, skill learning, consolidation, automaticity

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Introduction

Mild cognitive impairment (MCI) is a transition stage between normal age-related cognitive decline and the more serious symptoms of dementia caused by, for example, Alzheimer's disease. According to the American College of Physicians, MCI affects about 20% of the population over 70 years of age. Many who develop MCI eventually develop Alzheimer's disease, although some will remain stable or might even return to normal (Roberts et al., 2008). Of those with MCI, 12-15% will develop the signs of dementia within a year and about 50% will progress to dementia within five years (Gauthier et al., 2006). The characteristic symptoms of MCI are impaired memory functions during learning or recall, impaired attention and information processing evidenced by the speed with which these functions are executed, flawed executive functions, and perceptual motor-skill and language-expression disturbances (e.g., word finding). MCI is diagnosed if at least two of these symptoms are present for at least two weeks (Grundman et al., 2004; Petersen et al., 1999; Portet et al., 2006; Tariska, Kiss, Mészáros, & Knolmayer, 1990). MCI produces greater than age appropriate memory impairment but in all other aspects the individual functions well. Most often, learning skills and the ability to recall new information are affected to the highest extent. Brain imaging research shows dysfunction in the medial temporal lobe (MTL), including the hippocampal formation in MCI (Dickerson & Sperling, 2008; Jack et al., 1997) but other areas might also be affected (Rombouts et al., 2009). Memory tests have established that certain forms of explicit memory and learning, such as delayed recall and list learning, decline in MCI (Grundman et al., 2004; Leube et al., 2008; Petersen et al., 1999). However, the question of how implicit learning is affected by MCI has received less attention (Nagy et al., 2007; Negash et al., 2007). Properties of implicit learning and its consolidation could be useful in the dissociation of MCI from healthy age-related changes and also could contribute to a better understanding of the formation and consolidation of sequence acquisition, specifically the role of the MTL and hippocampus in these processes.

Explicit or declarative memory is accessible to conscious recollection, including facts and episodes (for example remembering events explicitly). It is defined by voluntary mechanisms which rely more on attentional resources. Non-declarative memory relies more on automatic, non-conscious/implicit processes including habituation, conditioning, motor and perceptual skills (for example playing piano). According to Squire and his colleagues, explicit or declarative memory can be linked to the brain's medial-temporal area, while the implicit or non-declarative processes fall outside these areas (Squire, 1998; Squire & Zola, 1996). Nevertheless, others showed that areas in the MTL including hippocampus also play a role in implicit learning (Albouy et al., 2008; Chun & Phelps, 1999; for critics, see Manns & Squire, 2001; Poldrack & Rodriguez, 2003).

The focus in our study is primarily on implicit sequence learning which underlies the acquisition of not only motor but also cognitive and social skills (Lieberman, 2000; Nemeth et al., 2011; Romano-Bergstrom, Howard, & Howard, 2012). Most models of sequence learning (Doyon, Bellec, et al., 2009; Okihide Hikosaka et al., 1999; O. Hikosaka et al., 2002) emphasize the role of the frontal-striatal-cerebellar system, while the role of the MTL and related structures (e.g., hippocampus) remains inconclusive (Albouy et al., 2008; Schendan et al., 2003) Simon, Vaidya, Howard, & Howard, 2012). Negash and his colleagues (Negash et al., 2007) have conducted the first and only research to address this topic so far, in which they investigated the effect of MCI on implicit learning. They used two implicit learning paradigms: the Serial Reaction Time (SRT; M. J. Nissen & Bullemer, 1987) to measure sequence learning, and the Contextual Cueing Task (Chun & Jiang, 1998) to measure visuospatial configuration learning. Despite the similarity in implicitness of these tasks, they call on two different neural systems; previous studies showed greater involvement of MTL in the Contextual Cueing (Chun & Jiang, 1998; Manns & Squire, 2001) compared to the SRT task, which is primarily mediated by the previously mentioned frontal-striatal-cerebellar system (Curran, 1998; Gomez-Beldarrain, Grafman, Pascual-Leone, & Garcia-Monco, 1999; Honda et al., 1998; Willingham et al., 2002). Negash, Petersen et al.'s results revealed that individuals with MCI, although generally slower, showed similar sequence learning to the controls; however, learning was impaired in the Contextual Cueing task. These findings implicate that the MTL system, including the hippocampal formation is involved in MCI, while the frontal-striatal-cerebellar system is involved to a lesser extent (Negash, Petersen, et al., 2007).

While Negash et al. (2007) used a deterministic 8-element sequence, we take the task one step further. Here we use a modified version of the SRT task, the Alternating Serial Reaction Time (ASRT) task (J. H. Howard, Jr. & Howard, 1997), which enables us to separate general skill learning and sequence specific learning. General skill learning refers to the increase in speed as the result of practice and it is relatively independent from sequence structure, while sequence-specific learning refers to the acquisition of sequence-specific knowledge, which results in relatively faster responses for events that can be predicted from the sequence structure versus those that cannot. Most research, including the Negash et al.'s (2007) study cited above, has not distinguished these because the tasks used make it difficult to do so. In classical SRT tasks used also by Negash et al. (2007), the structure of a sequence is deterministic, with the stimuli following a simple repeating pattern as in the series

213412431423, where numbers refer to distinct events. In contrast, in the ASRT task (J. H. Howard, Jr. & Howard, 1997; Remillard, 2008), repeating events alternate with random elements. This means that the location of every second stimulus on the screen is determined randomly. If, for instance, the sequence is 1234, where the numbers represent locations on the screen, in ASRT the sequence of stimuli will be 1r2r3r4r, with r representing a random element. The sequence is thus 'better hidden' than in the deterministic SRT task and it is also possible to track sequence-specific learning continuously by comparing responses to the random and sequence elements. This structure is called probabilistic second-order dependency (Remillard, 2008) because to predict element 'n' we need only to know element n-2, regardless of element n-1. In this way, the representations of the probabilistic sequences are more abstract and the acquisition of the sequences is also a statistical learning process. One of the outstanding questions in the literature of implicit learning is if there are functional differences in how implicit learning develops in motor versus cognitive tasks (Ashby, Turner, & Horvitz, 2010; Foerde et al., 2008). The fact that probabilistic sequences with their statistical properties are more ambiguous due to certain transitions being dictated by a context defined by remote events (Remillard, 2008) suggests that learning these sequences might result in more abstract representations than in deterministic sequence learning tasks (for another view see Keele, Ivry, Mayr, Hazeltine, & Heuer, 2003). Moreover, several studies showed that probabilistic sequence learning is related not only to motor, but also to perceptual processes (Song, Howard, & Howard, 2008; Nemeth, Hallgato, Janacsek, Sandor, & Londe, 2009; Hallgato, Gyori-Dani, Pekar, Janacsek, & Nemeth, 2013). Based on these considerations, probabilistic sequence-specific learning is presumed to be related relatively more to cognitive skills, while general skill learning is presumed to be related relatively more to motor skills in this specific design. It is a particularly interesting issue how MCI affects the performance on these two aspects of learning.

In the development and stabilization of memory representation for sequences, the processes of consolidation and reconsolidation, are particularly important (Rickard, Cai, Rieth, Jones, & Ard, 2008; Tucker, McKinley & Stickgold, 2011; Walker, Brakefield, Hobson, & Stickgold, 2003). During the acquisition of sequences we are learning and recalling and reactivating the sequence elements continuously. Recalling or reactivating a previously consolidated memory makes it once again fragile and susceptible to interference, therefore requiring periods of reconsolidation (Walker, et al., 2003). These circle processes make possible the continued refinement and reshaping of previously learned motor or cognitive skills in the context of ongoing experience. In experimental designs (fingertapping or SRT tasks) and partly in real-life situations, we are learning sequences arranged in blocks which are separated by shorter or longer time periods. In the beginning of the blocks we reactivate the already consolidated memory traces. Rickard et al. (2008) and Brawn et al. (2010) showed that the separate analysis of the different parts of the learning blocks is crucial in understanding the consolidation of sequence learning. For example, if we analyze only the first part of each of the learning blocks, we can find greater sequence learning effects by controlling the reactive inhibition (i.e., the inhibiting effect of fatigue on learning (Rickard, et al., 2008). These effects can be particularly relevant in a cognitive impaired population such as MCI. It is important to highlight, however, that Rickard et al. (2008) and Brawn et al. (2010) used explicit and not implicit sequence learning. Thus the question can be raised whether the pattern of results is the same for implicit learning. We hypothesize dissociation between explicit and implicit sequence learning because several factors, such as fatigue and attentional resources, affect the two types of learning differently (Squire & Zola-Morgan, 1996; Nissen & Bullemer, 1987; Janacsek & Nemeth, 2013).

It is also a relevant issue that sequence learning does not occur only during practice - online periods - but also between practice periods – during offline periods. The process that occurs during the offline periods is referred to as consolidation and is typically revealed either by increased resistance to interference and/or by improvement in performance, following an offline period (Krakauer & Shadmehr, 2006). The nucleus caudate and ventricle putamen, which are part of the fronto-striato-cerebellar network, play important roles in sequence consolidation (Albouy et al., 2008; Debarnot et al., 2009; Doyon, Bellec, et al., 2009; Doyon & Benali, 2005; Lehericy et al., 2005). More recent studies also emphasize the role of the hippocampus in the consolidation of sequence knowledge: for example, Albouy and colleagues (2008) found hippocampus activity using a 24-hour delay interval between the learning and testing session. MCI is an ideal avenue to solve the puzzle of sequence consolidation because of the above mentioned neurocognitive background of this cognitive impairment. Although there are several studies focusing on the consolidation of explicit processes in MCI (Westerberg et al., 2012), to our knowledge no study has investigated the effect of a 24-hour offline period on implicit sequence learning in this population so far.

In this study, we investigated sequence-specific and general skill learning in individuals with MCI. In this way we could indirectly investigate the role of the hippocampus and related MTL structures in this learning mechanism. A probabilistic sequence learning task was set up in a prolonged way in order to map the development and consolidation of memories for sequences. We had two main questions here: 1) to which extent can the individuals with MCI learn raw probabilities implicitly, 2) how within-block effects contribute to sequence learning performance. For the second question we hypothesized that the beginning of the learning blocks reflects the processes in which we are picking up high and low frequency triplets and reactivating/recalling the sequence information learned in the previous blocks. As reactivation/recall processes are shown to be related to the hippocampus and related structures (Gelbard-Sagiv, Mukamel, Harel, Malach, & Fried, 2008; Xue et al., 2010), we expected weaker learning performance in MCI based on the first half of the blocks compared to the second half of the blocks.

Materials and methods

Participants

Seventeen MCI patients and 17 healthy elderly controls participated in the experiment. Diagnoses of MCI were established via a consensus meeting of at least two clinical neurologists and a neuropsychologist using various examinations and tests (e.g., basic laboratory tests, brain MRI, clinical evaluation, Mini Mental State Examination - MMSE). Controls were individuals who: (1) were independently functioning community dwellers, (2) did not have active neurological or psychiatric conditions, (3) had no cognitive complaints, (4) demonstrated a normal neurological behavior, (5) were not taking any psychoactive medications (Negash, Petersen, et al., 2007).

The MCI and the control group were matched on age ($M_{MCI} = 61.82$, $SD_{MCI} = 7.70$; $M_{control} = 57.82$, $SD_{control} = 8.47$), years of education ($M_{MCI} = 13.35$, $SD_{MCI} = 2.21$; $M_{control} = 14.18$, $SD_{control} = 2.38$) and gender (14 and 15 females, respectively). The groups differed in performance on the MMSE ($t(32) = -6.31$, $p < 0.001$): the mean score was 26.91 (SD = 1.69, range 25-28) for the MCI group and 29.69 (SD = 0.48, range 29-30) for the controls. All participants provided signed informed consent agreements and received no financial compensation for their participation. The examinations were conducted at the neuropsychiatric office of the Aladár Petz County Research Hospital.

Procedure

The ASRT task was administered in two sessions separated by a 24-hour interval. Participants were informed that the main aim of the study was to find out just how extended practice affected performance on a simple reaction time task. Therefore we emphasized performing the task as fast and as accurate as they could. They were not given any information about the regularity that was embedded in the task.

In the first session the ASRT consisted of 20 blocks. As one block took about 1.5-2 minutes, the first session took approximately 30-40 minutes. Between blocks, participants received feedback on the screen about their overall reaction time and accuracy, then had a rest of between 10 and 20 sec before starting a new block. Session 2 lasted approximately 22-30 minutes, as the ASRT consisted of 15 blocks.

The computer program selected a different ASRT sequence for each participant based on a permutation rule, such that each of the six unique permutations of the 4 possible stimuli occurred. Consequently, six different sequences were used across participants while the sequence within participants was identical during Session 1 and Session 2 (J. H. Howard, Jr. & Howard, 1997; Nemeth et al., 2010).

The Alternating Serial Reaction Time (ASRT) Task

Sequence learning was measured by the "Catch the dog" version (Nemeth, et al., 2010) of the ASRT task (J. H. Howard, Jr. & Howard, 1997). In this ASRT task, a stimulus (a dog's head) appears in one of four empty circles on the screen and participants have to press the corresponding button when it occurs. The computer is equipped with a special keyboard with four heightened keys (Y, C, B, and M on a Hungarian keyboard; equivalent to Z, C, B, M on a US keyboard), each corresponding to the circles in a horizontal arrangement.

Unbeknownst to participants, the appearance of stimuli follows a predetermined order. As stimuli are presented in blocks of 85 stimuli, the first five button pressings are random for practice purposes, then an 8-element alternating sequence (e.g., 2r3r1r4r, where numbers represents the four circles on the screen and r represents random elements) repeats ten times. Because of this structure, some triplets or runs of three consecutive events occur more frequently than others. For example, in the above illustration, 1_4, 2_3, 3_1, and 4_2 (where "_" indicates the middle element of the triplet) 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_3 or 4_1 would occur less frequently because in this case the third element could only be random. Following previous studies, we refer to the former as high-frequency triplets and the latter as low-frequency triplets. Note that the final event of high-frequency triplets is therefore more predictable from the initial event when compared to the low-frequency triplets (also known as non-adjacent second-order dependency (Remillard, 2008). Therefore, for each stimulus we determined whether it was the last element of a high- or low-frequency triplet.

There are 64 possible triplets (4^3, 4 stimuli combined for three consecutive events) in the task. Out of these triplets, 16 are high frequency triplets, each of them occurring on approximately 4% of the trials, about 5 times more often than the low-frequency triplets. Thus, approximately 64 % of all trials are high-frequency triplets and the remaining 36 % of trials are low-frequency ones.

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 (D. V. Howard et al., 2004; J. H. Howard, Jr. & Howard, 1997; Song, Howard, & Howard, 2007). In addition, general skill learning is revealed in the ASRT task in the overall speed with which people respond, regardless of the triplet types. Thus, we are able to obtain measures of both sequence-specific and general skill learning in the ASRT task.

Statistical analyses

To facilitate data processing, the blocks of ASRT were organized into epochs of five blocks. The first epoch contains blocks 1-5, the second blocks 6-10, etc. (Barnes et al., 2008; Bennett, Howard, & Howard, 2007). As participants' accuracy remained very high (98.1 % for the MCI and 99.2 % for the control group) throughout the test (similarly to previous studies, e.g., J. H. Howard, Jr. & Howard, 1997; Nemeth, et al., 2010), we focused on reaction time (RT) for the analyses reported. For RTs, we calculated medians for correct responses only, separately for high and low frequency triplets and for each participant and each epoch.

To compare the overall learning between the groups, RTs were analyzed by a mixed design ANOVA on the 7 epochs of Session 1 and 2 with TRIPLET (2: high vs. low) and EPOCH (1-7) as within-subjects factors and GROUP (MCI vs. control) as a between-subjects factor. For exploration of offline changes in the 24-hour delay period, a similar ANOVA was conducted including only the last epoch of Session 1 and the first epoch of Session 2. All significant results are reported together with the η^2_p effect size and Greenhouse Geisser ε correction factors where applicable. Planned comparisons and post hoc analyses were conducted by Fisher's LSD pairwise comparisons.

Results

Do the MCI and the control group differ in overall sequence learning?

The ANOVA revealed significant *sequence-specific learning* (indicated by the significant main effect of TRIPLET: $F(1, 32) = 18.50$, $\eta^2_p = .37$, $p < .001$) such that RTs were faster on high than on low frequency triplets (Figure 2.9.1A). The groups differed in the extent of this sequence-specific learning (shown by the significant TRIPLET x GROUP interaction:

$F(1, 32) = 8.31$, $\eta^2_p = .21$, $p = .007$): the MCI group was 2.80 ms faster on high than on low frequency triplets ($p = .32$) while this difference was 14.20 ms for the controls ($p = .001$). Thus, only the controls acquired the sequence-specific knowledge overall.

The ANOVA also revealed *general skill learning* (shown by the significant main effect of EPOCH: $F(6, 192) = 42.70$, $\eta^2_p = .57$, $p < .001$), such that RTs decreased across epochs, irrespective of the triplet type. This decrease was slightly different for the groups (EPOCH x GROUP interaction: $F(6, 192) = 2.33$, $\eta^2_p = .07$, $p = .078$): RTs decreased steeper in the MCI group (153 ms from the first epoch to the last epoch) than in the controls (95 ms). This difference was mainly caused by the MCI group's relatively slower RTs in the first epoch compared to that of the controls (790 vs. 692 ms, $p = .07$). This difference diminished for the last epoch (647 vs. 607 ms, $p = .41$). Other interactions were not significant (ps > .17).

Although the MCI and the control group performed with similar RTs (main effect of GROUP: $F(1, 32) = 1.99$, $p = .17$), we re-ran our analyses using z-transformed RTs to confirm our findings. The ANOVA revealed sequence-specific learning (significant main effect of TRIPLET: $F(1, 32) = 43.77$, $p < .001$) with significantly smaller learning for the MCI than for the control group (TRIPLET x GROUP interaction: $F(1, 32) = 4.01$, $p = .05$). After the z-transformation, the EPOCH x GROUP interaction was not significant ($F(6, 192) = 1.26$, $p = .31$), suggesting a similar level of general skill learning in the two groups.

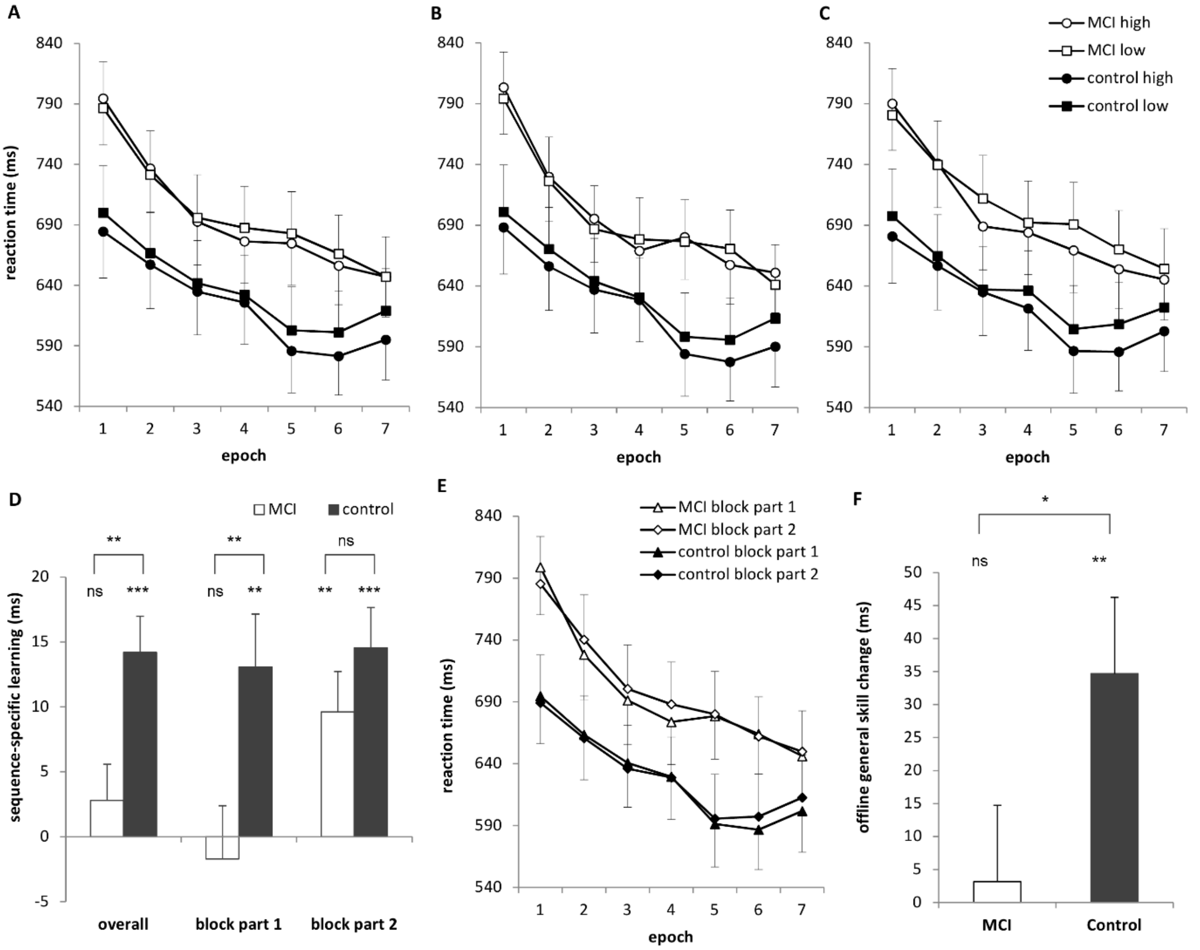

Figure 2.9.1. A) Sequence learning across 7 epochs (35 blocks) for the MCI and control group. Circles represent RTs for high-frequency triplets and squares represent RTs for low-frequency triplets. **B)** Learning curves for the first part of each block and **C)** the second part of each block. **D)** Sequence-specific learning (measured by the RTs for the low- minus high-frequency triplets) for the MCI and control group is plotted for the overall, first block-part and second block-part learning measures. Overall, the MCI group did not show significant sequence-specific learning, which was caused mainly by the learning performance in the first part of the blocks. The learning performance in the second part of the blocks was similar in the groups. **E)** General reaction times are plotted for the first and second parts of the blocks for the MCI and control group, separately. The MCI group was slower in the second parts of the blocks compared to the first parts of the blocks, but only in Session 1. The control group showed a similar pattern, but in Session 2. **F)** Offline general skill changes (measured as the RT difference between Epoch 4 and Epoch 5, irrespectively of the triplet types) over the 24-hour delay are plotted for the MCI and the control group with significant offline improvement for the controls only. Error bars represent standard error of mean. ns – nonsignificant, * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

Is there any within-block effect on learning? Are these effects different in the MCI and the control group?

A fine-grained analysis of the data can give us a deeper insight into the mechanisms of the development of sequence representation; therefore, it can also help to better understand the above reported sequence-learning deficit in MCI compared to controls. Analyzing the learning data by splitting each block into two halves is an excellent approach for exploring these questions. Therefore we conducted a mixed design ANOVA on the data shown in Figure 2.9.1B-C with TRIPLET (2: high vs. low frequency), EPOCH (7: 1-7) and PART (2: first vs. second half of blocks) as within-subject factors and GROUP (2: MCI vs. control) as a between-subject factor.

The ANOVA revealed significant sequence-specific learning overall (main effect of TRIPLET: $F(1, 32) = 18.27$, $\eta^2_p = .36$, $p < .001$) with smaller learning for the MCI group compared to controls (4 vs. 14 ms; TRIPLET x GROUP interaction: $F(1, 32) = 5.62$, $\eta^2_p = .15$, $p = .02$; Figure 2.9.1D). Interestingly, taking the PART of the blocks into account, we found a significant TRIPLET x PART interaction ($F(1, 32) = 4.43$, $\eta^2_p = .12$, $p = .04$): the sequence-specific learning was greater in the second part of the blocks compared to the first part (6 vs. 12 ms). Although the TRIPLET x PART x GROUP interaction did not reach significance ($F(1, 32) = 2.62$, $\eta^2_p = .08$, $p = .12$), planned comparisons revealed that the controls showed a similar extent of sequence-specific learning in the first and the second part of the blocks (13 and 14.5 ms, $p = .73$). In contrast, the MCI group showed higher sequence-specific learning in the second part of blocks than in the first part (1.7 vs. 9.6 ms, $p = .01$). All of these learning measures were significant (ps < .004), except for the first part of the blocks in the MCI group ($p = .68$). Thus, the group difference in sequence learning that we found in the previous analysis was driven mainly by the first part of the blocks (Figure 2.9.2), where the extent of sequence-specific learning was different between groups ($p = .01$), while they were similar in the second part of the blocks ($p = .22$).

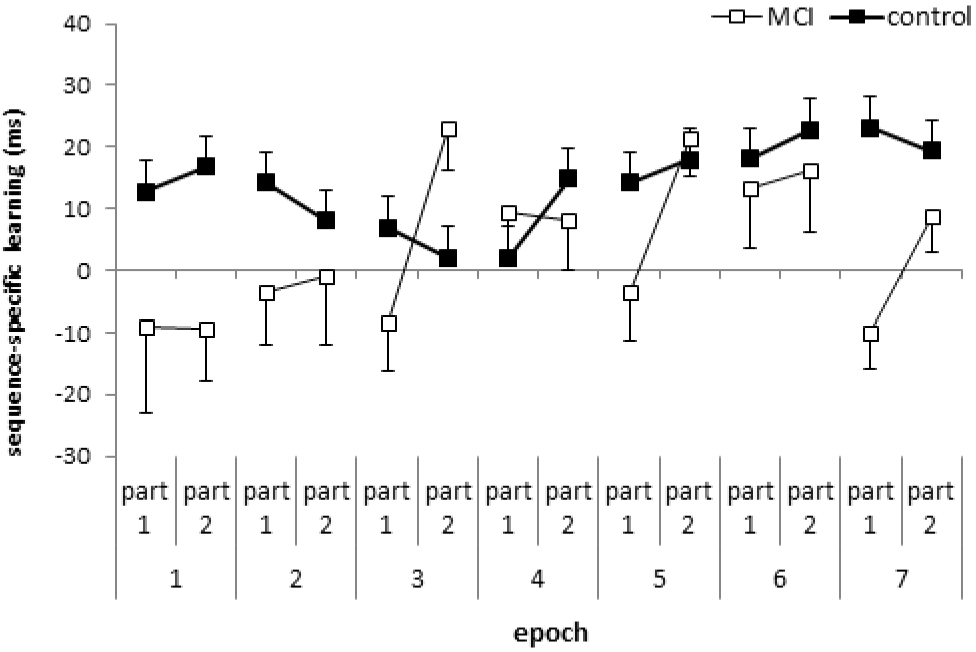

Figure 2.9.2. Sequence-specific learning (measured by the RTs for the low- minus high-frequency triplets) in the first and second parts of the blocks, collapsed into epochs, is plotted for the MCI and control group. Error bars indicate standard error of mean.

The ANOVA computed on z-transformed data confirmed our findings, as the TRIPLET x PART x GROUP interaction was significant (*F*(1, 32) = 5.93, *p* = .02). The MCI group showed significant sequence-specific learning only in the second halves of the blocks (*p* < .001) but not in the first halves (*p* = .29). In contrast, the controls exhibited significant sequence-specific learning both in the first and second parts of the blocks (*p*s < .001).

In the case of general skills, the ANOVA showed a significant improvement across epochs (main effect of EPOCH: *F*(6, 192) = 42.42, η^2_p = .57, *p* < .001), with a trend toward group differences (EPOCH x GROUP interaction: *F*(6, 192) = 2.46, η^2_p = .07, *p* = .06). This latter effect is similar to the results of the previous analysis finding that RTs decreased steeper in the MCI group (149 ms from the first epoch to the last epoch) than in the controls (87 ms). This difference, however, diminished when analyzing z-transformed data: EPOCH x GROUP interaction: *F*(6, 192) = 1.23, *p* = .32).

There was also a trend for different degrees of general skill improvement in the first and second part of the blocks (EPOCH x PART interaction: *F*(6, 192) = 1.91, η^2_p = .06, *p* = .08): the speed-up from the first to the last epoch was 123 ms when analyzing only the first parts of the blocks, while it was slightly smaller in the case of the second parts of the blocks (106 ms).

This was caused mainly by being faster in the second half of the blocks at the beginning of the task (737 vs. 746 ms in the first epoch), with a reverse pattern for the end of the task (631 vs. 624 ms in the last epoch). This effect remained and even became stronger after z-transforming the RTs (EPOCH x PART interaction: $F(6, 192) = 6.80$, $p < .001$).

Groups further detailed this picture (significant EPOCH x PART x GROUP interaction: $F(6, 192) = 2.22$, $\eta^2_p = .07$, $p = .04$; Figure 2.9.1E) as the MCI group was 12 ms faster in the first parts of the blocks compared to the second parts in Session 1 ($p = .004$) but showed similar RTs in Session 2 (1 ms difference between the RTs of the first and second parts of the blocks, $p = .73$). In contrast, the control group performed the task with similar RTs in Session 1 (2.6 ms difference, $p = .51$) but was 8.6 ms faster at the beginning of the blocks compared to the second parts in Session 2 ($p = .01$). This difference, however, disappeared when using z-transformed data (EPOCH x PART x GROUP interaction: $F(6, 192) = .02$, $\underline{p} = .33$). No other main effects of interactions were significant (*p*s > .21).

Is there any change in learning in the 24-hour delay?

For the exploration of the offline changes in the 24-hour delay period, ANOVA was conducted with TRIPLET (2: high vs. low frequency) and EPOCH (2: the last epoch of Session 1 and the first epoch of Session 2) as within-subject factors and GROUP (2: MCI vs. control) as a between-subject factor.

The ANOVA revealed sequence-specific learning (indicated by the significant main effect of TRIPLET: $F(1, 32) = 19.68$, $\eta^2_p = .38$, $p < .001$) which was retained across the sessions (TRIPLET x EPOCH interaction: $F(1, 32) = 0.51$, $\eta^2_p = .02$, $p = .48$). The groups did not differ either in overall sequence-specific knowledge (TRIPLET x GROUP interaction: $F(1, 32) = .19$, $\eta^2_p = .01$, $p = .67$) or in the offline change of this knowledge between the sessions (TRIPLET x EPOCH x GROUP: $F(1, 32) = 1.63$, $\eta^2_p = .05$, $p = .21$).

In contrast, there was an offline improvement in general skills (main effect of EPOCH: $F(1, 32) = 5.32$, $\eta^2_p = .14$, $p = .028$), with faster RTs in the first epoch of Session 2 compared to the last epoch of Session 1 (Figure 2.9.1F). This change was slightly different between groups (EPOCH x GROUP interaction: $F(1, 32) = 3.69$, $\eta^2_p = .10$, $p = .064$): the MCI group showed no between-session speed-up (3 ms, $p = .79$) while the controls did (34.7 ms, $p = .005$). The ANOVA on z-transformed RTs confirmed this result, showing a weaker consolidation of general skills for the MCI than for the control group (marginally significant EPOCH x GROUP interaction: $F(1, 32) = 3.85$, $p = .06$). Other interactions involving the GROUP were not significant ($ps > .71$).

We also conducted a consolidation analysis taking the first and second parts of the blocks into account and found similar results, with significant group differences in offline general skill changes (EPOCH x GROUP interaction: $F(1, 32) = 4.30$, $\eta^2_p = .12$, $p = .046$). The offline change in general skills was significant for the control group (35.8 ms faster at the beginning of Session 2 compared to the end of Session 1, $p = .004$) but not significant for the MCI group (1.65 ms difference, $p = .89$).

Discussion

Our goal was to investigate the acquisition of sequence knowledge in Mild Cognitive Impairment. We used a task that allows differentiating between sequence-specific and general skill learning. At first, based on the standard ASRT analysis we found that individuals with MCI showed weaker implicit probabilistic sequence learning than the healthy aged group. However, once we dug deeper and considered only the second half of each learning block, we found similar learning performances in the MCI as in the healthy aged group. Thus, the overall sequence-specific learning in MCI depends on which part of each learning block is considered. In the case of general reaction time, the MCI group was faster in the first part of the blocks compared to the second part in Session 1. The healthy aged group showed a similar pattern, except in Session 2. We were able to demonstrate that general skill consolidation over a 24-hour delay period was different in MCI and in the healthy aged group. The latter group showed offline improvement in general reaction time while the MCI group did not show this speed-up effect. We believe our study to be the first one that uses an implicit sequence learning task with second-order dependency in individuals with MCI.

Our results partly contradict but partly support the findings of Negash and his colleagues (2007), who showed learning with a deterministic SRT task in MCI but not in the Contextual Cueing task (Chun & Jiang, 1998). The impaired sequence learning that we found in MCI could be due to the more difficult and more complex sequence structure in our task, compared to the one used by Negash et al. (2007). Another possibility is that deterministic and probabilistic sequence learning tasks are qualitatively different: the latter with their statistical properties are more ambiguous due to higher order associations in which a current event is predicted not by the preceding event but by the context of more remote events (Cohen et al., 1990; Keele et al., 2003). Thus, our result of impaired sequence learning in MCI is more similar to the results of the Contextual Cueing task in Negash et al.'s study. The Contextual Cueing task relies on visual search (e.g. find a horizontal T on the screen), which is generated within a background of some repeated distractor configuration (unknown to participants) providing a contextual cue to the location of the target. As a result of practice, the participants detect the target-stimulus in repeated configurations faster than in random configurations, even though they are not aware of the repeated distractors. This task calls on different neural systems than the SRT task (MTL-hippocampus vs. the frontal-striatal-cerebellar system; Chun & Jiang, 1999; Curran, 1998; Gomez-Beldarrain, et al., 1999; Honda, et al., 1998; Manns & Squire, 2001; Willingham, et al., 2002). Despite these differences in the involvement of different neural systems, our results suggest that the MTL and the hippocampal formation are also somehow involved in probabilistic sequence learning measured by the ASRT task. The within-block analysis can help us specify the nature of this involvement.

The result that the overall sequence-specific learning depends on whether we consider the first part or the second part of each learning block supports the suggestion of Rickard et al. (2008), who stressed the importance of the within-block position effect. However, we did not find a fatigue effect within the block in either group. Moreover, in the MCI group we showed significant overall sequence-specific learning when only taking the second part of the learning blocks into account, suggesting a warm-up or priming effect (cf. Figure 2.9.2). The fact that the MCI group exhibited significant sequence-specific learning in the second part of the blocks but not in the first part, suggests that the processes are qualitatively different between the first and the second part of the learning blocks. In the beginning of the blocks we have to recall and reactivate the sequence structure partly learned already in the previous blocks. The second part of each block might be responsible for the utilization and/or proceduralization of the sequence knowledge. Based on these assumptions, we claim that the detection of probabilities in the reactivation/recall phase is somehow impaired in MCI. In addition, as MTL structures, including the hippocampus are primarily affected in MCI (Dickerson & Sperling, 2008; Jack, et al., 1997) and we found impaired sequence learning in the first part of learning blocks, the reactivation/recall of the sequence knowledge in the beginning of the blocks might be more MTL-dependent than in the second part. However, more studies are needed to confirm this suggestion.

These within-block effects also open a window to the similarities and dissimilarities between learning performance on the ASRT and the Contextual Cueing task. Although several neuropsychological studies have showed dissociation on the performance of these tasks, showing evidence of the different neurocognitive background (Barnes, Howard, Howard, Kenealy, & Vaidya, 2010; Howard, Howard, Japiske, & Eden 2006; Negash, Boeve, et al., 2007; Simon et al., 2011), our results suggest that these two tasks somehow involve similar processes but only in the first part of the ASRT blocks. In this part of the blocks the reactivation/recall of the previously learned regularities is prominent. Moreover, in order to recover the previously acquired sequence memories, picking up the context information of the items at the beginning of each block is essential. As previous studies showed, these processes are linked to the hippocampus and related MTL structures (Gelbard-Sagiv et al., 2008; Wood, Dudchenko, Robitsek, & Eichenbaum, 2000; Xue et al., 2010). In sum, learning performance in specific parts of the ASRT seems to rely on the involvement of the hippocampus and related MTL structures.

Regarding general reaction times, we found that in Session 1 the MCI group was faster in the first part of the learning blocks compared to the second part, while this pattern was present for the control group in Session 2. Generally, slower RTs at the end of learning blocks than at the beginning suggest a build-up of fatigue within each block. This fatigue effect emerges later for the controls than for the MCI group. These results partly support the findings of Rickard and his colleagues (2008), who showed this fatigue effect masking some aspects of learning performance in a fingertapping task. Since the MCI group showed significant sequence-specific learning in the second half of the blocks, in spite of the fact that they were generally slower due to fatigue, we can claim that the impaired sequence-specific learning in the MCI group is not caused by this fatigue effect in our study.

Previous studies argue that the caudo-ventral putamen (Debarnot et al., 2009; Doyon & Benali, 2005) and the hippocampus (Albouy, et al., 2008) can both play a role in the consolidation of sequence learning. Since MTL structures, including the hippocampus, are mostly affected by MCI (Dickerson & Sperling, 2008), our results that the MCI group did not forget the sequence in the 24-hour delay period might suggest that these structures are not essential for the consolidation of sequence-specific knowledge, though they might affect the consolidation of general skill learning. This latter finding is in line with previous studies using fingertapping tasks (e.g., Walker et al., 2003), suggesting that general skill learning in our design might share similar neurocognitive background with motor learning. However, future studies need to clarify these similarities.

In sum, our findings that the detection of probabilities in the reactivation/recall phases of the learning is impaired in MCI draw attention to the importance of the hippocampus and the related MTL structures in the development of sequence memory representation. Our results add detail to the picture regarding background processes of sequence acquisition and consolidation and refine Negash et al.'s (2007) final conclusion that adapting to environment is preserved in MCI. Based on our findings, we believe that the reactivation phase of the detection of probabilities is impaired in MCI. If further studies with different methods, including functional brain mapping, confirm this view, it could lead to the development of more focused and more effective prevention and rehabilitation programs for minor and major cognitive disorders.

Acknowledgment

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2.10 Implicit probabilistic learning in Obstructive Sleep Apnea[11]

Abstract

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.

Keywords: Obstructive Sleep Apnea, sequence learning, implicit learning, sleep, memory

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1. Introduction

Implicit sequence learning occurs when information is acquired from an environment of complex stimuli without conscious access either to what was learned or to the fact that learning occurred (D. V. 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., 2012); 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 (D. V. Howard et al., 2004). Most models and empirical studies of sequence learning highlight the role of the basal ganglia (Daselaar, Rombouts, Veltman, Raaijmakers, & Jonker, 2003; Okihide Hikosaka et al., 1999; Kincses et al., 2008; A. Rieckmann et al., 2010; Sefcsik et al., 2009), while the role of hippocampus, frontal and parietal areas remains inconclusive (Albouy et al., 2008; Gheysen, Van Opstal, Roggeman, Van Waelvelde, & Fias, 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 comprehensively characterized 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 hypoxia which leads to repetitive arousals from sleep, thus disturbing the normal sleep pattern (Banno & Kryger, 2007). In OSA only a few studies 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 used sequence learning (e.g. Finger-Tapping, Serial Reaction Time Task) to measure implicit motor learning. Lojander, Kajaste, Maasilte & Partinen (1999) demonstrated poor performance on Finger-Tapping task in apnea patients. By contrast, other studies (Archbold, Borghesani, Mahurin, Kapur, & Landis, 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 ones 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., 2007b). To our knowledge this kind of complex implicit sequence learning has not been studied yet 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 (for opposite findings see Bo, Jennett, et al., 2011; Feldman et al., 1995; Frensch & Miner, 1994; Kaufman et al., 2010; McGeorge, Crawford, & Kelly, 1997; Unsworth & Engle, 2005). The frontal lobe-related attentional processes are the mostly influenced by the disrupted sleep architecture (Hobson, 2009; Muzur, Pace-Schott, & Hobson, 2002). Therefore we can predict that the working memory is more affected compared to less attention demanding implicit sequence learning in OSA.

2. Methods and Materials

2.1. 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). 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). Respiratory Disturbance Index 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, 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 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.

2.2. Tasks

Alternating Serial Reaction Time (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, Janacsek, Londe, 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 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, and then they had 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 such 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 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, Janacsek, Londe, et al., 2010; Song et al., 2007b), 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 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 Remillard, 2008) (Figure 2.10.1).

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 (D. V. Howard et al., 2004; Song et al., 2007b). 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., 2007b) 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.

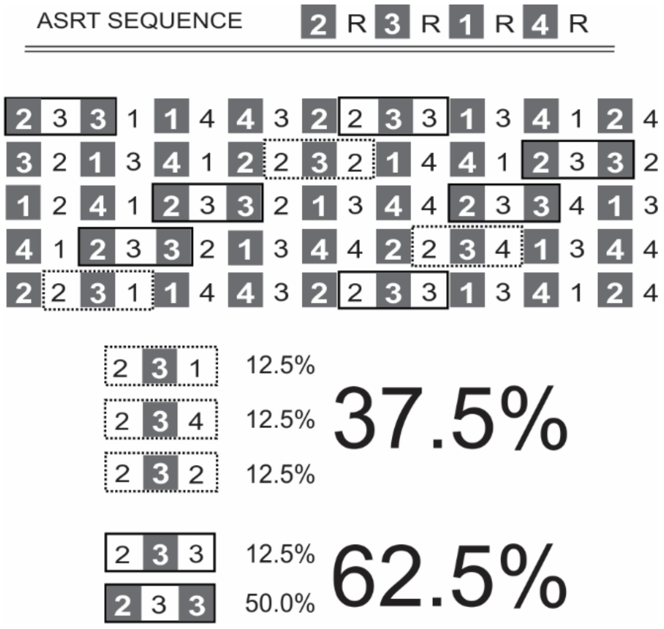

Figure 2.10.1. In a typical ASRT sequence, there are more frequent (high frequency) triplets and less frequent (low frequency) triplets. In other words, if we know what were the last two elements of the sequence (in this case

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.

Listening Span Task

The working memory performance was measured by the Listening Span Task (Daneman & 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.

2.3. 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.

2.4. 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 reaction time (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, Janacsek, Londe, et al., 2010; Song et al., 2007b) 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 (D. V. Howard et al., 2004). So by eliminating them, we can assure that any high versus low frequency differences are due to learning and not to pre-existing tendencies.

3. Results

3.1. ASRT analysis

A mixed design ANOVA was conducted on the 4 epochs of the data shown in Figure 2.10.2 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, η_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 x GROUP interaction: F(1,38)=1.21, η_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, η_p=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, η_p=0.001, p=0.98).

The TRIPLET x EPOCH and TRIPLET x EPOCH x GROUP interactions were not significant (F(3,114)=1.60, η_p=0.04, p=0.19; F(3,114)=0.78, η_p=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, η_p=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).

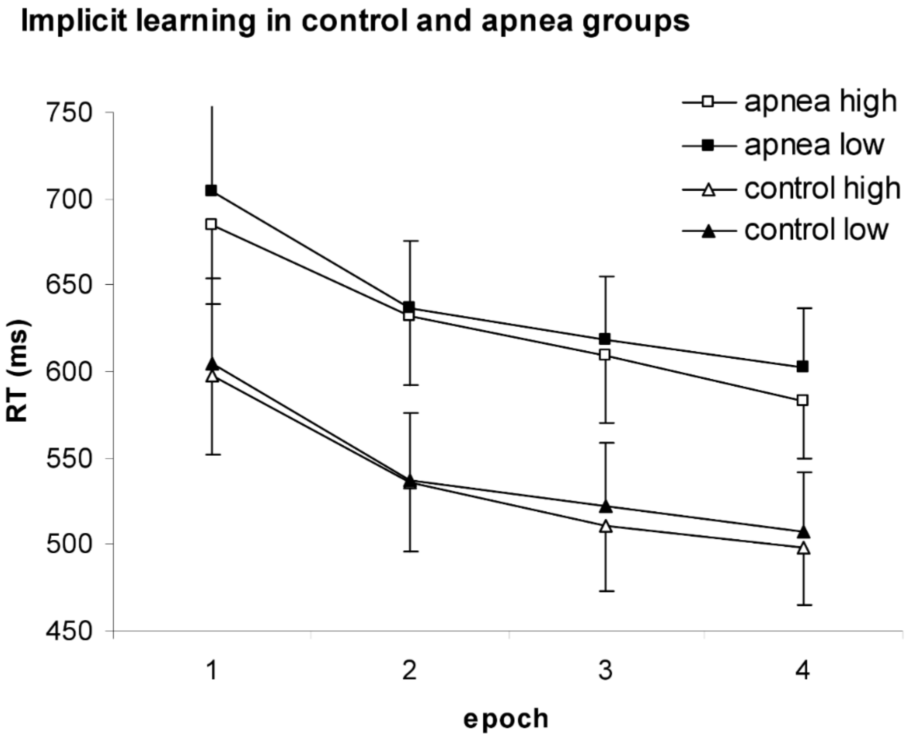

Figure 2.10.2. Implicit sequence learning in control and sleep apnea group. Both groups showed general skill learning as well as sequence-specific learning. There were no group differences. Error bars indicate standard error of mean.

3.2. 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 2.10.3).

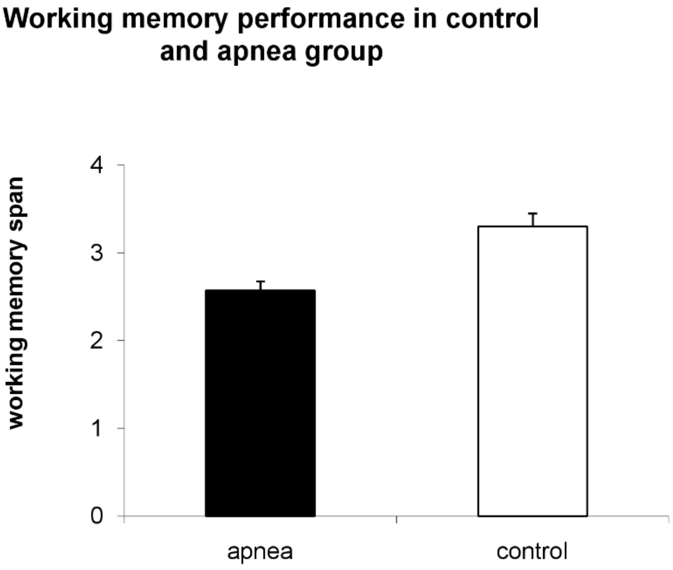

Figure 2.10.3. Working memory performance in control and sleep apnea group. The working memory span of the sleep apnea group was significantly lower compared to the control group. Error bars indicate standard error of mean.

4. Discussion

Our goal was to investigate whether implicit sequence learning is impaired in OSA. We used the ASRT task that 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 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 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 selectively study sub-cortical learning functions, with the least cortical influence (Fletcher et al., 2005). ASRT task uses more complex sequence structure then Finger-Tapping Tasks (probabilistic vs. deterministic). On neuroanatomical level ASRT is associated even more to basal ganglia rather than motor cortex in contrast to the Finger-Tapping Task where motor cortex plays a critical role in learning performance (Walker, Stickgold, Alsop, Gaab, & Schlaug, 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 SRT task (Van Der Werf, Altena, Vis, Koene, & Van Someren, 2011). This latter result is consistent with Genzel et al. (2009) who found that disturbed SWS and REM phases did not impair sequential Finger-Tapping performance.

According to the studies on the relationship between cognitive functions and normal and disrupted sleep (Naegele et al., 2006; Robertson, Pascual-Leone, & Press, 2004; Song et al., 2007b; Stickgold et al., 2002) we can suggest that the sleep has impact on the structures related to the more attention demanding processes still more 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 & 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 & Kryger, 2007). Further investigations are needed to clarify this question.

Taken together, this study found 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 in develop more sophisticated diagnostic tools and more effective rehabilitation programs. Beyond the OSA our findings well complement sleep-dependent memory consolidation models (Doyon, Korman, et al., 2009; Robertson, 2009; Stickgold & Walker, 2007), and draw attention the fact that the sleep might have less influence on the structures related to implicit processes.

Acknowledgement

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3. FACTORS UNDERLYING THE CONSOLIDATION OF PROBABILISTIC LEARNING

3.1 The role of sleep in the consolidation of implicit probabilistic learning[12]

Abstract

The influence of sleep on motor skill consolidation has been a research topic of increasing interest. In this study we distinguished general skill learning from sequence-specific learning in a probabilistic implicit sequence learning task (Alternating Serial Reaction Time) in young and old adults before and after a 12-hour offline interval which did or did not contain sleep (pm-am and am-pm groups respectively). The results showed that general skill learning, as assessed via overall RT, improved offline in both the young and older groups, with the young group improving more than the old. However, the improvement was not sleep-dependent, in that there was no difference between the am-pm and pm-am groups. We did not find sequence-specific offline improvement in either age group for either the am-pm or pm-am groups, suggesting that consolidation of this kind of implicit motor sequence learning may not be influenced by sleep.

Keywords: implicit sequence learning, Alternating Serial Reaction Time Task, aging, sleep, memory consolidation.

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[12] Published in Nemeth, D., Janacsek, K., Londe, Z., Ullman, M. T., Howard, D. V., & Howard Jr, J. H. (2010). Sleep has no critical role in implicit motor sequence learning in young and old adults. *Experimental Brain Research*, *201*(2), 351-358.

Most models of motor skill learning (Doyon, Bellec, et al., 2009; Okihide Hikosaka et al., 1999; O. Hikosaka et al., 2002) emphasize the role of the basal ganglia and the cerebellum, while the role of hippocampus remains inconclusive (Albouy et al., 2008; Schendan et al., 2003). Motor skill learning can be differentiated into phases (first rapid phase, second slower phase), into modalities (motor, visual, visuo-motor, auditory, etc.) and into consciousness types (implicit and explicit) (Doyon, Bellec, et al., 2009).

Skill learning does not occur only during practice, in the so-called *online* periods, but also between practice periods, during the so-called *offline* periods. The process that occurs during the offline periods is referred to as consolidation, and is typically revealed either by increased resistance to interference, and/or by improvement in performance, following an offline period (Krakauer & Shadmehr, 2006). Special attention has been given to the role of sleep; for instance references are made to *sleep-dependent consolidation* (Walker & Stickgold, 2004) suggesting that performance improves more when the offline period includes sleep than when it does not. Several studies showed the critical role of sleep in skill learning consolidation (S. Fischer et al., 2002; Stickgold, James, & Hobson, 2000; Walker et al., 2002).

Nonetheless, the results concerning offline improvements have been mixed, and recent reviews (Doyon, Korman, et al., 2009; Robertson, Pascual-Leone, & Press, 2004; Siengsukon & Boyd, 2008; Song, 2009; Song et al., 2007b) indicate that whether or not offline improvements occur at all, and whether they are sleep-dependent, varies with factors such as phase of learning, awareness, the formation of contextual associations and type of information to be learned, as well as the age of the participants. For example, a recent study by Doyon et al. (Doyon, Korman, et al., 2009) found offline sleep-dependent consolidation for a finger tapping sequence-learning task, but no sleep-dependent consolidation for a visuomotor adaptation task in young people. In another study which used a sequence learning task, Spencer et al. (Spencer et al., 2007) showed that while young adults revealed sleep-dependent offline improvements, healthy older adults did not.

The present study focuses on another distinction that has received little attention in the literature on offline learning, i.e., on separating general skill learning from sequence-specific learning. *General skill learning* refers to increasing speed as the result of practice with the task, while *sequence-specific learning* refers to acquisition of sequence-specific knowledge, which results in relatively faster responses for events that can be predicted from the sequence structure versus those that cannot. Most research, including the Doyon and Spencer studies cited above, has not distinguished these, because the tasks used make it difficult to do so.

Here we use a modified version of the Serial Response Time (SRT) task, the Alternating Serial Reaction Time (ASRT) task (Howard and Howard 1997) which enables us to separate general skill learning and sequence specific learning. General skill learning is reflected in the overall reaction time, whereas sequence-specific learning is reflected in the difference between the reaction time of unpredictable, random and predictable, sequence events. In classical SRT tasks the structure of a sequence is deterministic with the stimuli following a simple repeating pattern as in the series 213412431423, where numbers refer to distinct events. In contrast, in the ASRT task (Howard and Howard 1997; Remillard 2008) repeating events alternate with random elements. This means that the location of every second stimulus on the screen is determined randomly. If, for instance, the sequence is 1234, where the numbers represent locations on the screen, in the ASRT the sequence of stimuli will be 1R2R3R4R, with R representing a random element. The sequence is thus better hidden than in the classical SRT task and it is also possible to track sequence-specific learning continuously by comparing responses to the random and sequence elements. This structure is referred to as a probabilistic second-order dependency (Remillard 2008). The structure is second-order in that for pattern trials, event *n-2* predicts event *n*. It is probabilistic in that these pattern trials occur amidst randomly determined ones. In addition, participants do not generally become aware of the alternating structure of the sequences even after extended practice, and sensitive recognition tests indicate that people do not develop explicit knowledge of which event-sequences are more likely to occur (Howard & Howard 1997; Howard et al. 2004; Song et al. 2007). Thus, even the predictable alternate events appear unpredictable to the participants.

In a previous study using a different version of the ASRT, Song et al. (2007) studied offline learning in young adults. People were tested on three sessions with an equivalent period of wake or sleep between sessions. Results showed evidence of offline improvement of general skill learning after a period of wakefulness, but no evidence of improvement following sleep. In contrast, there was no evidence of offline improvement in sequence-specific learning following either a period of sleep or wake.

Few studies have examined skill consolidation in older adults. Several studies have shown that old adults show implicit sequence-specific learning comparable to young adults for simple repeating patterns in the SRT task (Howard and Howard 1989; Howard and Howard 1992; Frensch and Miner 1994). However, more recent studies have reported that although older adults can learn higher-order sequence structure, they show age-related deficits in doing so (Curran 1997; Howard and Howard 1997; Howard et al. 2004). It was interesting to find that in one study using a version of the ASRT task, old persons were able to learn even third-order dependencies (1RR2RR3 where R refers to random), although they learned less than the young control group (Bennett et al. 2007). The few studies that have investigated offline learning in old persons (Spencer et al. 2007; Siengsukon and Boyd 2009a; Siengsukon and Boyd 2009b) did not find offline improvement. Spencer et al. (2007) used an implicit deterministic SRT in order to examine the effect of sleep specifically. Neither offline improvement, nor a sleep effect was shown in elder subjects. However, neither Siensukon et al. (Siengsukon and Boyd 2009b) nor Spencer et al. (Spencer et al. 2007) distinguished general skill learning from sequence-specific learning in their tasks. The ASRT task has been shown to yield offline general skill learning, but not offline sequence-specific learning in young adults (Song et al. 2007), and so it is important to distinguish between these two aspects of skill learning in older adults.

The aim of the current study is to compare offline learning and the role of sleep in young and old adults 1) in implicit sequence-specific learning and 2) in general skill learning separately.

Materials and methods

Participants

The young group consisted of 25 right-handed subjects (between 19-24 years of age, average age: 21, SD: 1.2; 9 male/16 female) randomly assigned to the DAY group (n = 11) or the NIGHT group (n = 14). The aged group consisted of 24 older right-handed subjects (between 60-80 years, average age: 69.75, SD: 7.25; 8 male/16 female) randomly assigned to the DAY group (n = 13) or the NIGHT group (n = 11). Subjects did not suffer from any developmental, psychiatric or neurological disorders, did not have sleeping disorders, and all reported having 7-8 hours of sleep a day. All subjects provided signed informed consent agreements and received no financial compensation for their participation.

All participants completed a short sleep questionnaire which was adapted from the one used in Song et al, 2007. It consisted of 4 questions regarding sleep quantity and quality (“How many hours did you sleep?”, “How would you rate your sleep quality?”, “How long does it take you to fall asleep?” and “How often do you wake up in the middle of the night or early morning?”), and each question was asked separately for sleep in general, and for the previous night’s sleep. Each question could be scored between 0-3 (the larger the score, the worse the sleep characteristic). A sleep score was calculated for general sleep and for previous night’s sleep for each subject by summing across the 4 questions (so the sum scores could vary between 0-12). Across all participants, the overall mean sleep score for general characteristics was 3.49

(SD=1.28), and that for previous night's characteristics was 2.38 (SD=1.09). There were no significant differences among the groups (DAY and NIGHT, YOUNG and AGED; all *p*'s>0.48).

Procedure

All groups completed two sessions: a learning phase (Session 1) and a testing phase (Session 2). These sessions were separated by a 12-hour interval. For the DAY group the first session was in the morning (between 7 – 8 am) and the second session was in the evening (between 7 – 8 pm), with the opposite for the NIGHT group (see Fig 1A).

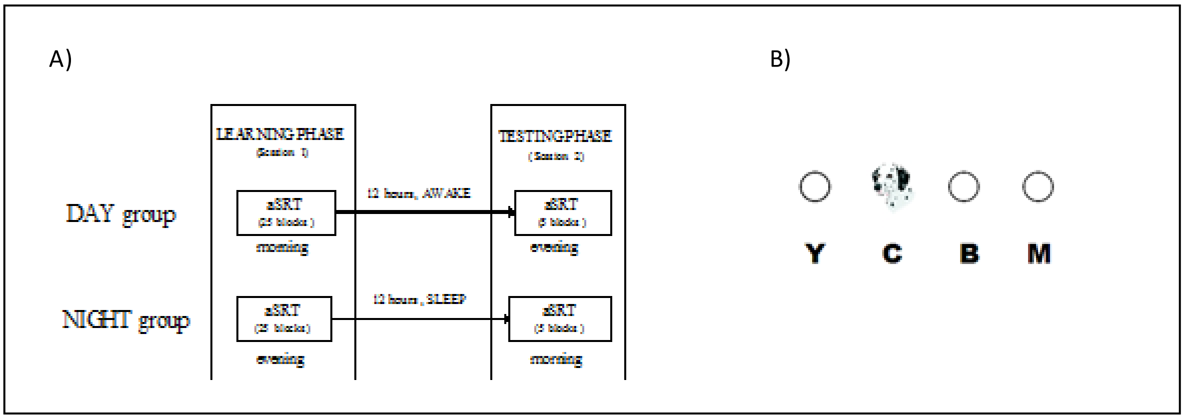

Figure 3.1.1. A) Design of the experiment: The DAY group stayed awake between the two sessions, whereas the 12 hours delay included sleep in the NIGHT group. **B)** Example of stimulus displayed on the screen (top), and the corresponding keys (below).

Alternating Serial Reaction Time (ASRT) Task

We used a modification of the original ASRT task (Howard and Howard 1997) in which a stimulus (a dog head) appeared in one of the four empty circles on the screen and the subject had to press the corresponding key when it occurred (see Fig 1B). The computer was equipped with a special keyboard with four heightened keys (Y, C, B and M), each corresponding to the circles. Before beginning people were read detailed instructions as they followed along on the screen. We emphasized that the aim was to try to respond as quickly and as correctly as possible.

During the first session (learning phase) the ASRT consisted of 25 blocks, with 85 key presses in each block - the first five button pressings were random for practice purposes, then the eight-element alternating sequence (e.g., 1r2r3r4r) was repeated ten times. Following

Howard et al (1997) stimuli were presented 120-ms following the previous response. As one block took about 1.5 minutes, the first session took approximately 30-35 minutes. Between blocks, the subjects received feedback about their overall reaction time and accuracy on the screen, and then they had a rest of between 10 and 20 sec before starting a new block. The second session (testing phase) lasted approximately 10 minutes as the ASRT consisted only of 5 blocks to examine the offline changes of previously acquired knowledge. The number of key presses per block and the event timing were the same as Session 1.

The computer program selected a different ASRT series for each subject 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 subjects, but the sequence for a given subject was identical during Session 1 and Session 2.

To explore how much explicit knowledge subjects acquired about the task, we administered a short questionnaire (the same as Song et al., 2007) after the second session. 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 young or older groups reported noticing the sequence in the task.

Statistical analysis

As there is a fixed sequence in the ASRT with alternating random elements (for instance 1r2r3r4r), some triplets or runs of three events occur more frequently than others. For example, in the above illustration 1x2, 2x3, 3x4, and 4x1 would occur often whereas 1x3 or 4x2 would occur infrequently. Following previous studies, we refer to the former as high-frequency triplets and the latter as low-frequency triplets. For the analyses reported below, as in previous research (e.g., J. H. Howard et al. 2004; 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 subjects, and people often show pre-existing response tendencies to them (D. V. Howard et al. 2004; Soetens et al. 2004), so eliminating them ensures that any high versus low frequency differences are due to learning and not to pre-existing tendencies. Thus, pattern trials are always high frequency, whereas one-fourth of random trials are high frequency by chance. 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. Thus, each low-frequency triplet occurs on approximately 0.8% of the trials whereas each high-frequency triplet occurs 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.

Earlier results 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). 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 obtain measures of both sequence-specific and general skill learning in the ASRT task.

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 blocks 6-10, etc. (Bennett et al. 2007; Barnes et al. 2008).

Subjects' accuracy remained very high throughout the test (average over 97% for all groups), as is typical (e.g. Howard and Howard, 1997), and so we focus on RT for the analyses reported. For reaction time (RT), we calculated medians for correct responses only, separately for high and low frequency triplets and for each subject and each epoch.

Results

Online learning during session 1

To investigate learning during the first session (learning phase) a mixed design ANOVA was conducted on the first 5 epochs of the data shown in Figure 3.1.2A, 2B with (TRIPLET: high vs. low) and (EPOCH: 1-5) as within-subjects factors, and AGE GROUP (young vs. old) and DAY GROUP (day vs. night) as between-subjects factors. There was significant sequence-specific learning (indicated by the significant main effect of TRIPLET: F(1,45)=93.08, MSE=89.57, p<0.0001) such that RT was faster on high than low frequency triplets (Bennett et al. 2007). There was also general skill learning (shown by the significant main effect of EPOCH: F(4,180)=42.49, MSE=1928.87, p<0.0001), such that RT decreased across epochs.

The only significant effect involving DAY GROUP was an interaction with AGE GROUP: F(1,45)=5.89, MSE=24677.52, p=0.02. Subsequent t-tests revealed that the young group who had been tested first in the AM had overall faster RTs than those tested first in the PM (389 vs 414 ms): t(23)=2.09, p=0.048, whereas the older groups showed the reverse pattern, even though the difference was not significant for the older groups (614 vs 574 ms), t(22)=1.59, p=0.12. It is not clear why these differences occurred, but they are not important for interpreting the offline results in that they do not involve learning. Importantly, no other effects involving DAY GROUP approached significance (all p's > 0.26).

The ANOVA also revealed three significant age differences, all consistent with previous findings. First, young people responded faster overall than older (shown by the main effect of AGE GROUP: F(1,45)=192.87, MSE=24677.52, p<0.0001). Second, young people revealed greater sequence-specific learning than older (shown by the TRIPLET x AGE GROUP interaction: F(1,45)=7.68, MSE=89.57, p=0.008). Third, old people showed more general skill learning than young people (shown by the EPOCH x AGE GROUP interaction: F(4,180)=16.41, MSE=1,928.87, p<0.0001). Older adults' RT decreased from 675 ms in Epoch 1 to 550 ms in Epoch 5, while young subjects' decreased from 420 ms to 380 ms. Subsequent TRIPLET x EPOCH x DAY GROUP mixed design ANOVAs, conducted separately for each age group confirmed that when examined alone, each age group showed both general skill learning and sequence-specific learning. For the young group there was a main effect of EPOCH, F(4,92)=6.54, MSE=32.53, p<0.0001, and of TRIPLET, F(1,23)=124.00, MSE=56.65, p<0.0001, and an EPOCH x TRIPLET interaction, F(4,92)=6.54, MSE=32.54, p<0.0001. For the old group there were main effects of EPOCH, F(4,88)=28.21, MSE=3749.98, p<0.0001, and of TRIPLET, F(1,22)=16.80, MSE=123.99, p=0.0005.

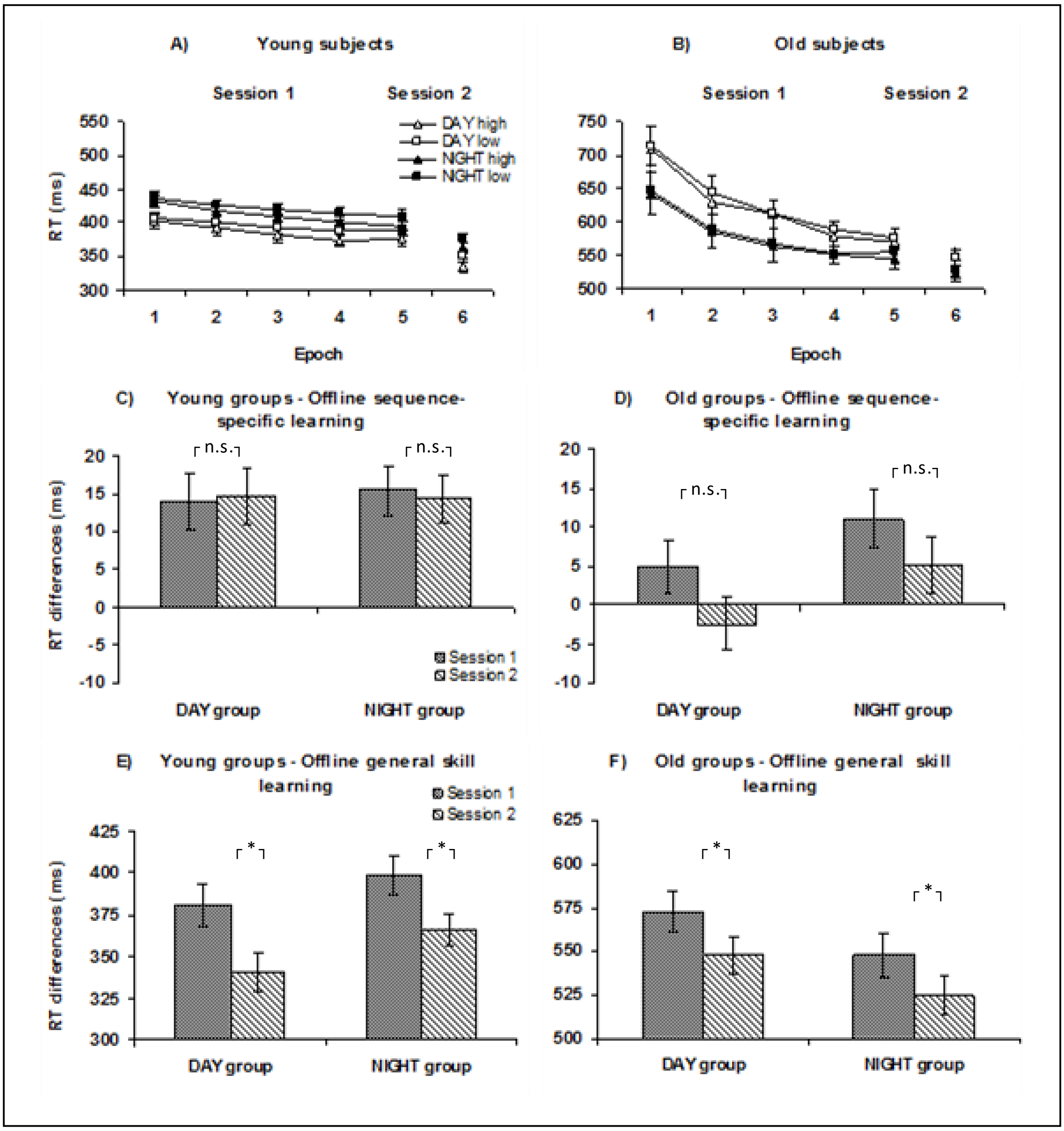

Figure 3.1.2. A-B: Results of Session 1 (epoch 1-5) and Session 2 (epoch 6) for young (A) and old (B) subjects. The differences between the high (open and filled triangles) and low frequency (open and filled squares) triplets indicate sequence-specific learning, whereas the decrease of reaction time (regardless of triplet types) indicates general motor skill learning. In Session 1 all groups showed significant sequence-specific and general motor skill learning, but the extent of sequence-specific learning was smaller for old subjects than for young ones. **C-D:** Results of offline sequence-specific learning for young (C) and old adults (D). The learning index of the last epochs of Session 1 does not differ significantly from that of the first epochs of Session 2 neither in young (C) nor in old groups (D), suggesting that there is no offline sequence-specific improvement (n.s. – non-significant). There were no differences between day and night groups (no sleep effect). **E-F:** Results of offline general motor skill learning for young (E) and old groups (F). Offline general motor skill learning (calculated by the difference between the last epoch of Session 1 and the first epoch of Session 2, regardless of triplet types) appeared both in young (E) and

old (F) groups (stars mark the significant differences). There were no differences between day and night groups (no sleep effect). Error bars indicate SEM.

Offline sequence-specific learning

To define the index for offline sequence-specific learning, we calculated the RT difference for the low minus high frequency triplets for the last epoch of Session 1. This index shows the magnitude of learning at the end of the first session. Then, similarly, we calculated the RT difference for the low minus high frequency triplets for the first epoch of Session 2. These difference scores (shown in Figure 3.1.2C, 2D) were submitted to a mixed design ANOVA with SESSION (1-2) as a within-subject factor and AGE GROUP (young vs. old) and DAY GROUP (day or night) as between-subject factors. Thus, any off-line consolidation of sequence-specific learning would be revealed by main effects and/or interactions with SESSION. However, the only significant effect obtained was a main effect of AGE GROUP, F(1.45)=14.57, MSE=166.27, p=0.0004, reflecting the smaller magnitude of sequence-specific learning in both sessions in the old group compared to the young. No other main effects or interactions approached significance (all p’s > 0.15). Thus, there was no evidence of offline changes (improvement or decrease) of sequence-specific knowledge regardless of age or day group.

Offline general skill learning

To examine offline general skill learning we calculated the overall RT (combined across triplet types) for the last epoch of Session 1 and the first epoch of Session 2; the greater the decrease from Session 1 to Session2, the larger the offline general skill learning was. These RTs (shown in Figure 3.1.2E, 2F) were submitted to a mixed design ANOVA with SESSION (1-2) as a within-subjects factor and AGE GROUP (young vs. old) and DAY GROUP (day or night) as between subject factors. Thus, any offline consolidation of general skill would be revealed by main effects and/or interactions with SESSION. This ANOVA revealed a main effect of AGE GROUP, reflecting the overall longer RTs for the old than the young group, F(1,45)=257.64, MSE=2933.77, p<0.0001, and an AGE GROUP x DAY GROUP interaction, F(1,45)=4.32, MSE=2933.77, p=0.043. This interaction again reflects the finding from Session 1 that the young AM group has overall faster RT than the young PM group, t(48)=2.02, p=.048, whereas the old groups show the reverse pattern (though the AM/PM difference is only marginally significant for the older groups) t(46) = 1.80, p=0.08. The fact that this effect does not interact with SESSION (p>0.65) suggests that we happened to assign slightly faster young people to the AM group; if this were a true time of day effect then we would not expect it to occur for the young AM group for both of their testing sessions. Further, Song et al (2007) included diurnal control groups in their study, and were able to rule out time of day effects as explanations for offline changes in the ASRT.

More important for present purposes, this ANOVA revealed evidence of offline improvement of general skill in that the main effect of SESSION was significant, F(1,45)=96.76, MSE=228.62, p<0.0001, reflecting the faster overall RTs for Session 2 compared to those at the end of Session 1. The SESSION x AGE GROUP interaction was also significant, F(1,45)=4.20, MSE=228.62, p=0.046, indicating that the young group (mean improvement of 36 ms) showed more offline improvement than the old (mean improvement of 24 ms). Importantly, there was no evidence that offline consolidation depended upon sleep, in that no interactions involving session and day group approached significance (p's > 0.45). It is also possible that the improvement in RT reflects a release from fatigue rather than consolidation *per se*. However, studies that have included a fatigue control group (Walker et al. 2002; Spencer et al. 2006) suggest that this interpretation is unlikely.

Subsequent SESSION x DAY GROUP mixed design ANOVAs, conducted separately for each age group confirmed that when examined alone, each age group showed consolidation of general skill learning, in that both groups yielded significant main effects of SESSION: for the young group, F(1, 23)=105.23, MSE=156.03, p<0.0001, and for the old group F(1,22)=22.40, MSE=304.50, p<0.0001. Thus, although the overall ANOVA had revealed that the young group showed more offline improvement of general skill than the old, the old group did show significant consolidation of general skill as well.

This evidence for offline consolidation of general skill relies on comparing RT on epoch 6 to that on epoch 5, so it is possible that the faster RT on epoch 6 is simply due to learning that occurred during epoch 6. To rule out this possibility, we compared the difference in overall RT between the last two epochs within Session 1 (epoch 4 minus 5) versus the change across sessions (epoch 5 minus 6). This difference was significantly greater across sessions than within sessions for both age groups, t(23) = 6.665, p <.0001 for old, and t(24) = 13.164, p<.0001 for young. This suggests that the offline effects we observed were not simply due to continued learning.

Discussion

The novelty of the present research compared to previous studies of consolidation in older adults (Siengsukon & Boyd, 2009b; Spencer et al., 2007) is that 1) it used probabilistic second-order sequences, and 2) it dealt separately with general skill learning and sequence-specific learning. In our study, we focused on the offline changes and the role of sleep in implicit sequence learning in young and elder adults. In the case of general skill learning we found significant offline improvement for both the young and older groups, although the effect was significantly smaller in the old than in the young. We found no evidence that this improvement was sleep-dependent in that there were no differences between the day (am-pm) and the night (pm-am) groups in the offline consolidation of general skill. In the case of sequence-specific learning, we found no offline improvement, in that the RT difference between low and high frequency triplets (i.e., the triplet type effect) did not increase between sessions for any group. This occurred despite the fact that there was significant sequence-specific learning for all groups in Session 1. In addition, the fact that the triplet type effect did not decrease significantly between sessions for any of the groups, suggests that sequence-specific knowledge was well-consolidated for all groups. However, circadian effects could still have different effects on the consolidation processes.

The results of the young group in the current study largely confirm the results of Song et al. (2007) in finding no evidence of any offline improvement of sequence-specific skill, and extend them to older adults. However, Song et al. (2007) found general skill improvement only in the no-sleep condition, whereas we found it in both conditions. The reason for this difference in findings is unclear. The most notable difference between our and Song's study is that we used less training in the learning phase (5 vs 9 epochs). The resulting greater skill learning in Song et al in the first session may have left less room overall for participants to show offline improvement.

Our results are similar to those of Spencer et al. (2007) and Siengsukon and Boyd (2009) in showing no sleep dependent consolidation in older adults. However, unlike these studies, which had detected no offline improvement at all in older adults, the current study shows clear evidence of significant offline improvement of general skill learning in older adults over periods of both sleep and wake. These previous studies differed from the present study in many ways, so it is difficult to identify the source of the different findings. For example, they used deterministic rather than probabilistic sequences and gave less training. Our results do suggest that offline improvement is reduced in old compared to young adults, and this may have made it difficult for the previous studies to detect any offline improvements in the older group.

The differences between our findings and those of earlier studies underscore that the role of sleep in offline consolidation is likely task dependent. This is consistent with the conclusions of Doyon et al. (2009), who found sleep benefits in a finger tapping sequence learning task, but not in a visuomotor adaptation task with young adults. Future studies should investigate which of the many task differences influence offline learning and sleep effects. Beyond that, the present findings demonstrate that it will also be important to distinguish general skill from sequence-specific learning. For example, it is possible that the offline improvements reported by Doyon et al (2009) in the finger tapping task reflect consolidation of general motor rather than sequence-specific skill. Given that these components are typically inseparable in finger tapping tasks, offline improvements in such studies might be falsely attributed to sequence learning. The present results from both young and old adults join Song et al's findings from young adults in suggesting that, at least in the version of the ASRT task used here, general skill, but not sequence-specific learning undergoes offline improvement. Given the likely importance of task factors mentioned above, future research must investigate whether this conclusion holds under other conditions, such as different amounts of initial training and other levels of sequence structure. It will also be useful to include diurnal control groups to ensure that circadian effects are not influencing consolidation in ways we could not detect.

Our findings well complement motor skill learning models (Hikosaka et al. 1999; Hikosaka et al. 2002; Doyon et al. 2009), and draw attention to the importance of separating general skill and sequence-specific learning during consolidation, and to the question of whether these two factors may be differently influenced by nervous system modifications caused by aging.

Acknowledgements

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3.2 Consolidation of implicit probabilistic learning in Obstructive Sleep Apnea[13]

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.

Keywords: sleep disruption, memory consolidation, general skill learning, sequence-specific learning, obstructive sleep apnea, implicit 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 stabile and resistant to interference and forgetting (Krakauer & Shadmehr, 2006). 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 (Axmacher, Draguhn, Elger, & Fell, 2009; Diekelmann & Born, 2010; Diekelmann, Wilhelm, & Born, 2009; Ficca & Salzarulo, 2004; S. Fischer et al., 2005). Sleep-related enhancement in declarative memory is clearly demonstrated (Steffen Gais et al., 2007; S. Gais & Born, 2004; Steffen Gais, Lucas, & Born, 2006), 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 (S. Fischer et al., 2002; Walker et al., 2002). By contrast, several recent studies failed to find sleep-related improvement in sequence learning (Nemeth, Janacsek, Londe, et al., 2010; Rickard et al., 2008; Song et al., 2007b; Urbain et al., 2013). 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 (Djonlagic, Saboisky, Carusona, Stickgold, & Malhotra, 2012; S. Fischer et al., 2002; Walker et al., 2002). In the present study, we used the Alternating Serial Reaction Time (ASRT) task (J. H. Howard, Jr. & Howard, 1997) 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 (Nemeth, Janacsek, Londe, et al., 2010; Song et al., 2007b).

Previous studies suggest that sleep disorders (e.g., insomnia) lead to weaker consolidation both of declarative and non-declarative memory (Backhaus et al., 2006; C. Nissen et al., 2006). 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 (Banno & Kryger, 2007). Deficits in working memory (Archbold et al., 2009; Nemeth et al., 2012), attention, executive functions (Bedard, Montplaisir, Richer, Rouleau, & Malo, 1991; Engleman, Kingshott, Martin, & Douglas, 2000; Naegele et al., 1995; Orth et al., 2005), short and long-term verbal and visual memory have been demonstrated in OSA (Cosentino et al., 2008; Naegele et al., 1995; Pierobon, Giardini, Fanfulla, Callegari, & Majani, 2008) indicating structural changes in brain circuits crucial for memory (Macey et al., 2008). Nevertheless, sequence learning has not been extensively characterized in OSA. Lojander, Kajaste, Maasilta & Partinen (1999) 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 (Wilde et al., 2007) and also on a more complex, probabilistic sequence learning task (Nemeth et al., 2012), 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 (Kloepfer et al., 2009) 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 (Djonlagic et al., 2012). 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 (Djonlagic et al., 2012)),

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 (Nemeth, Janacsek, Londe, et al., 2010; Song et al., 2007b), 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) (Daneman & Blennerhassett, 1984; Janacsek, Tanczos, Meszáros, & Nemeth, 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, Jennett, et al., 2011; Frensch & Miner, 1994). However there is also evidence that the two systems are independent of each other (Kaufman et al., 2010; McGeorge et al., 1997; 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. 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 (Nemeth, Janacsek, Londe, et al., 2010). 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 (Nemeth, Janacsek, Londe, 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. 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 (Nemeth, Janacsek, Londe, et al., 2010), 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 (Nemeth, Janacsek, Londe, et al., 2010).

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 (Nemeth, Janacsek, Londe, et al., 2010; Song et al., 2007b), 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 (2008)).

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 (D. V. Howard et al., 2004; Song et al., 2007b). 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 (2007b), Nemeth and colleagues (2010)) 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 (Nemeth, Janacsek, Londe, et al., 2010; Song et al., 2007b), 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 (D. V. Howard et al., 2004). 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 3.2.1A, 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^2_p 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 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 (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 ($F(1,32) = 32.34$, $\eta_p^2 = 0.5$, $p < 0 .001$), 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 3.2.1B-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 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.

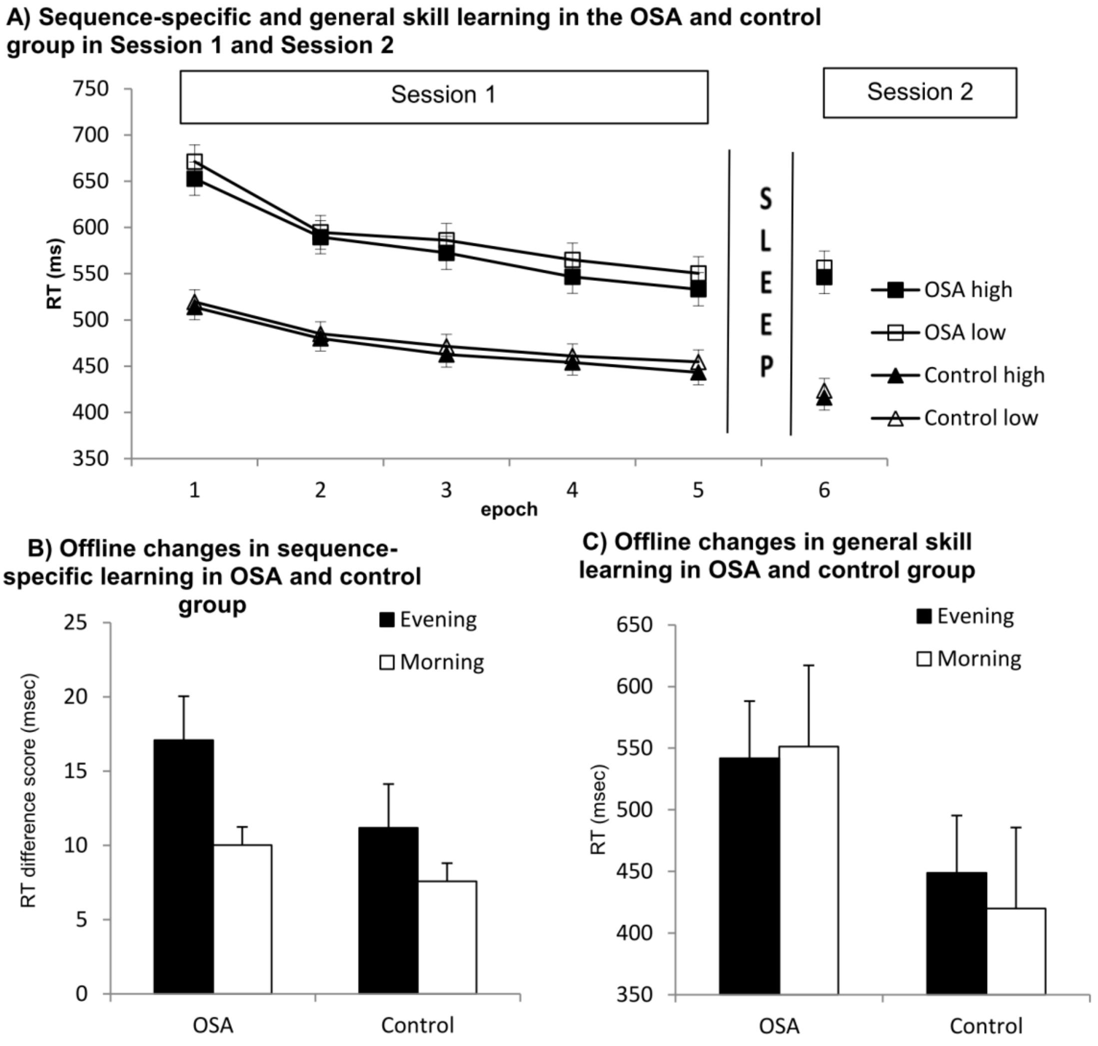

Figure 3.2.1. A) Results of sequence-specific and general skill learning in OSA and control group in Session 1 and Session 2: Although the OSA group was generally slower in Session 1, both groups showed significant sequence-specific and general skill learning. There were no differences in learning between 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.

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 (Lojander et al., 1999; Nemeth et al., 2012; Wilde et al., 2007). For example, Nemeth and colleagues (2012) and Csabi, Benedek, Janacsek, Katona & Nemeth (Csábi, Benedek, Janacsek, Katona, & Nemeth, 2013) 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 (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). Naegelé 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. 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. Kloepfer et al (Kloepfer et al., 2009) 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 (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 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 (Nemeth, Janacsek, Londe, et al., 2010; Song et al., 2007b). 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 (Song & Cohen, 2014) 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 (Beat Meier & 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 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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3.3 The dynamics of implicit skill consolidation in young and elderly adults[14]

Abstract

Implicit skill learning underlies not only motor but cognitive and social skills, it is therefore an important aspect of life from infancy to old age. We studied aging effects on the time course of implicit skill consolidation. Young and elderly adults performed a probabilistic implicit sequence-learning task before and after a 12-hour, a 24-hour and a 1-week offline interval. The task enabled us to separate the components of skill learning: 1) general skill and 2) sequence-specific learning. We found improvement of general skill for the young adults. The elderly adults also showed offline enhancement after the 12-hour offline period, revealing brain plasticity similar to young adults. This improvement disappeared in the 24-hour and the 1-week delay conditions. Regarding sequence-specific learning, no offline improvement was found in either age group and at either consolidation interval. In contrast, sequences-specific knowledge decreased in the elderly group independently of the delay. These results draw attention to the fact that consolidation is not a single process, rather there are multiple mechanisms in offline learning and they are differentially affected by time course and by aging.

Keywords: skill learning, implicit sequence learning, ASRT, aging, memory consolidation.

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Introduction

Skill learning can be differentiated by phases (rapid and slower), modalities, and whether or not it is conscious (implicit and explicit) (Doyon, Bellec, et al., 2009). Implicit skill learning occurs when information is acquired from an environment of complex stimuli without conscious access either to what was learned or to the fact that learning occurred (Reber, 1993). In everyday life, this learning mechanism is crucial for adapting to the environment and evaluating events. Implicit skill learning underlies not only motor but cognitive and social skills as well, it is therefore an important aspect of life from infancy to old age. Implicit skills remain essential to healthy functioning with the advancement of age in various contexts, such as social interactions, everyday habits or reading skills. Most models of motor skill learning (Doyon, Bellec, et al., 2009; Okihide Hikosaka et al., 1999; O. Hikosaka et al., 2002; Keele et al., 2003; Kincses et al., 2008) emphasize the role of the basal ganglia and the cerebellum. Skill learning does not occur only during practice, in the so-called *online* periods, but also between practice periods, during the so-called *offline* periods. The process that occurs during the offline periods is referred to as consolidation which means stabilization of a memory trace after the initial acquisition; it can result increased resistance to interference or even improvement in performance following an offline period (Krakauer & Shadmehr, 2006; Nemeth, Janacsek, Londe, et al., 2010; Robertson, 2009; Song, 2009). Understanding the time course of skill consolidation can help us reveal the nature of aging memory and age-related changes in brain plasticity.

Recent reviews conclude that offline changes vary with factors such as the phase and awareness of learning, the formation of contextual associations, the type of information to be learned, as well as the age of the participants (Brashers-Krug, Shadmehr, & Bizzi, 1996; N Deroost & E Soetens, 2006; Doyon, Korman, et al., 2009; L Jiménez, Vaquero, & Lupiáñez, 2006; Keele et al., 2003; Robertson, Pascual-Leone, & Press, 2004; Siengsukon & Boyd, 2008; Song, 2009; Song et al., 2007b). Studies on the time course of skill consolidation indicate that there is a “critical period” after the learning phase, which is necessary for the stabilization of memory traces. This time period depends on the task demand, and it varies from 1-2 hours (Robertson et al., 2005), to 5 hours (Shadmehr & Brashers-Krug, 1997; Shadmehr & Holcomb, 1997), or 6 hours (Walker, Brakefield, Hobson, & Stickgold, 2003). Using the Serial Reaction Time (SRT) task, which is a widely known sequence-learning paradigm, one study found that the offline enhancement increased with the length of delay (Press et al., 2005). In this SRT study no enhancement was found 1 hour after the learning phase, but significant enhancement was observed after 4 hours, which further increased after 12 hours. These results suggest that offline learning may be a dynamic process. However, this study examined only a shorter stretch of time, so the question can be raised, what happens in skill consolidation after more than 12 hours.

The modified version of SRT is the Alternating Serial Reaction Time (ASRT) task (J. H. Howard, Jr. & Howard, 1997), which enables us to separate general skill learning and sequence-specific learning. The sequence is better hidden than in the classical SRT task (eg. Press et al., 2005), thus improving the implicitness of the design (J. H. Howard, Jr. & Howard, 1997; Song et al., 2007b). Why are the properties of the ASRT interesting in everyday-life in aging? The key factor is the implicit nature of the task. In everyday-life we use explicit, conscious and implicit, non-conscious processes at the same time to do a task (e.g. typing on the computer, or learning a foreign language). These processes interact in cooperative and sometimes competitive ways (R. M. Brown & Robertson, 2007b; Poldrack & Packard, 2003; Song, Marks, Howard, & Howard, 2009) in order to optimize the memory performance (Ullman, 2004). It has long been known that there is age-related decline in explicit memory and executive functions (N Cowan, Naveh-Benjamin, Kilb, & Saults, 2006; F. Craik & Salthouse, 2000; F. I. Craik & Bialystok, 2006; Einstein & McDaniel, 1990). It is therefore possible that aged people can not acquire new skills on the same level as young adults, because of these weaker explicit processes, and not because of the impairment of pure implicit skill learning. In the ASRT task explicit memory processes and conscious awareness on sequence learning is almost totally eliminated. That’s why it can model implicit learning better than other tasks. So, in the case of intact learning in the ASRT task we can claim that everyday difficulties regarding skill learning are mainly due to weak explicit processes.

Several studies using the ASRT task demonstrated that older adults show age-related deficits in online skill learning (T. Curran, 1997; D. V. Howard et al., 2004; J. H. Howard, Jr. & Howard, 1997). However, little is known about the effects of aging on skill consolidation and its time course (Siengsukon & Boyd, 2009b; Spencer et al., 2007).

Previous studies using the ASRT task focused primarily on whether sleep affects skill consolidation and have concluded that these processes are not influenced by sleep (Nemeth, Janacsek, Londe, et al., 2010; Song et al., 2007b). For example, in a recent ASRT study, Nemeth et al. (2010) investigated implicit skill learning after 12-hour offline period. The novelty of this research compared to previous studies of consolidation in older adults (Siengsukon & Boyd, 2009b; Spencer et al., 2007) was that 1) it used probabilistic second-order sequences, and 2) it dealt separately with general skill and sequence-specific learning. They showed that general skill learning, as assessed via overall RT, improved offline in both the young and older groups, with the young group improving more than the old group. However, the improvement was not sleep-dependent, in that it was not relevant whether the 12-hour offline period included sleep or not. They did not find sequence-specific offline improvement in either age group, and similarly to general skill learning it was not influenced by sleep. However, this study did not examine the consolidation of skills after more than 12 hours in healthy aging.

The current experiment was designed to study the effects of aging on the offline time course of implicit skill learning. The present study goes beyond Nemeth et al (2010) and other previous studies (Press et al., 2005; Siengsukon & Boyd, 2009b; Spencer et al., 2007) by comparing the performance after 12-, 24-hour and 1 week delays from the initial learning session. We focused on the consolidation of implicit sequence-specific learning and, separately, general skill learning between young and elderly adults. Despite the results of previous studies which found greater improvement after longer offline periods (more after 12 hours compared to 4 hours, see Press et al. (2005) et al), it is less plausible that this is true for 12-, 24-hour and 1-week delays as well. Therefore we aim to determine a time point in a longer stretch of time at which improvement can still be observed in skill consolidation, and analyze its possible age-related differences.

Methods

Participants

Seventy-one young and 58 elderly right-handed adults participated in the experiment (for detailed data see Table 3.3.1). They were randomly assigned to the 12-hour, 24-hour or 1-week delay group (seventy percent of the 12-hour groups were also presented in the study of Nemeth et al. (2010)). Participants did not suffer from any developmental, psychiatric or neurological disorders, did not have sleeping disorders, and all reported having 7-8 hours of sleep a day. They gave informed written consent after the aims and procedures of the experiment were explained to them, and received no financial compensation for participation.

Table 3.3.1: Mean age, education and sex of young and elderly groups.

Group		Age (years)	Education (years)	Sex
Young	12 hrs (n=23)	20.83 (1.11)	13.48 (1.27)	8 male / 15 female
	24 hrs (n=31)	21.74 (4.15)	14.77 (2.13)	12 male / 19 female
	1 week (n=17)	19.88 (1.27)	13.65 (1.32)	3 male / 14 female
Elderly	12 hrs (n=23)	66.43 (6.18)	12.90 (3.26)	7 male / 14 female
	24 hrs (n=22)	67.36 (5.30)	13.84 (2.44)	5 male / 17 female

1 week (n=13)	65.15 (4.14)	14.23 (2.00)	6 male / 7 female

Procedure

There were two sessions in the experiment to examine the offline changes of implicit skill learning: a learning phase (Session 1) and a testing phase (Session 2) separated by a 12-, 24-hour or 1-week interval offline period (see Figure 3.3.1). Previous studies with similar tasks and experimental designs showed no time of day effect either on general reaction times or on learning measures (Nemeth, Janacsek, Londe, et al., 2010; Press et al., 2005; Robertson, Pascual-Leone, & Press, 2004; Song et al., 2007b), the time of testing was however counterbalanced across participants.

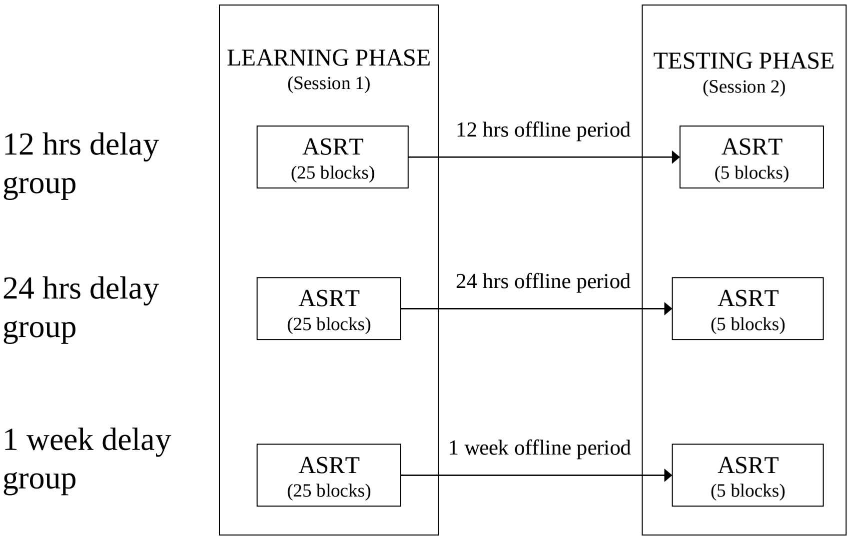

Figure 3.3.1: The design of the experiment

Alternating Serial Reaction Time (ASRT) Task

We used a modification of the original ASRT task (J. H. Howard, Jr. & Howard, 1997) in which a stimulus (a dog head) appeared in one of the four empty circles shown all the time on the screen (Nemeth, Janacsek, Londe, et al., 2010). Participants were instructed to press one of four possible response keys on an IBM PC keyboard as fast as they could. Each response key (Y, C, B or M on Hungarian keyboard) was assigned to one of the four stimulus locations on the screen.

In the ASRT task, repeating events alternate with random ones 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 repeating events, and R represents random stimulus events). This sequence structure has been termed *probabilistic second-order dependency* (Remillard, 2008), because to predict stimulus 'n' we need only to remember stimulus n-2 in the sequence, regardless of stimulus n-1. The repeating sequence in the ASRT task is thus 'better hidden' than in the classical SRT task, which uses deterministic sequences (D. V. Howard et al., 2004; J. H. Howard, Jr. & Howard, 1997; Song et al., 2007b).

During Session 1 (learning phase), the ASRT task consisted of 25 blocks, with 85 stimuli in each block. For practice purposes, the locations of the first five stimuli of each stimulus block were always random. These were followed by the eight-element sequence (e.g. 1R2R3R4R) repeating ten times. Following Howard and Howard's design (1997), stimuli were presented 120-ms after the response to the previous stimulus. Between stimulus blocks, the subjects received feedback about their overall reaction time and accuracy presented on the screen, and then they had a rest period of between 10 and 20 s before starting the next stimulus block. Session 2 (testing phase) consisted of only 5 stimulus blocks of the same type as in Session 1.

The computer program selected a different ASRT sequence for each subject based on a permutation rule such that each of the six unique permutations of the 4 repeating events occurred with equal probability (J. H. Howard, Jr. & Howard, 1997; Nemeth, Janacsek, Londe, et al., 2010). 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 administered a short questionnaire (the same as Song et al. (2007b) and Nemeth et al. (2010)) after the second session. 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 the participants' answers on a 5-point scale, where 1 meant "Nothing noticed" and 5 meant "Total awareness". None of the participants reported noticing the repeating sequence of the stimulus locations.

Statistical analysis

Because in ASRT a repeating sequence alternates with random events, some runs of three consecutive events (termed triplets) occur more frequently than others. For example, with the 1R2R3R4R sequence, 1x2, 2x3, 3x4, and 4x1 (where "x" denotes any location) would occur more often than e.g., 1x3 or 4x2. We refer to the former as *high-frequency* triplets and the latter as *low-frequency* triplets. The triplets including two consecutive repeating-sequence stimuli were always of high frequency triplets, whereas one-fourth of the triplets that included two consecutive random stimulus events were high-frequency by chance, the rest being low frequency. 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 results showed that as participants practice the ASRT task, they come to respond more quickly to the high- than to low-frequency triplets, thus revealing sequence-specific learning (D. V. Howard et al., 2004; J. H. Howard, Jr. & Howard, 1997; Song et al., 2007b). Therefore, sequence-specific learning (SSL) is reflected in the reaction time (RT) difference between low- and high-frequency triplets (Song et al., 2007b, 2008). The larger this SSL score, the greater the sequence-specific learning is. In addition, general skill learning is revealed in the ASRT task in the improving overall response speed, irrespective of the triplet types. 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. (Barnes et al., 2008; Bennett et al., 2007). Consequently, Session 1 consisted of 5 epochs, whereas Session 2 consisted of 1 epoch.

The accuracy of responses remained very high throughout the test (average over 97% for all groups), as is typical (e.g. Howard and Howard (1997) and Nemeth et al. (2010)). 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 – Session 1

To be able to investigate the offline changes, the learning in Session 1 must be similar in the groups. From this point of view the end of Session 1 is crucial (Nemeth, Janacsek, Londe, et al., 2010; Press et al., 2005; Song et al., 2007b). Therefore, sequence-specific learning (SSL) score was computed by reaction times on low minus high frequency triplets in Epoch 5 (Song et al., 2007b, 2008). The larger this difference, the greater the sequence-specific learning was. This score was submitted to a Univariate ANOVA with AGE GROUP (young vs. older) and DELAY (12, 24 hours or 1 week) as between-subject factors. The ANOVA revealed significant sequence-specific learning ($F(1,123)=136.69$, $MSE=157.95$, $\eta_p^2=0.53$, $p<0.00001$). Neither the main effects of AGE GROUP and DELAY, nor the AGE GROUP x DELAY interaction was significant (p’s>0.19), thus there were no differences in sequence-specific learning among age groups or delays at the end of Session 1(see Figure 3.3.2ab).

Regarding the general skill, a Univariate ANOVA was conducted on overall RT’s of Epoch 5 (collapsed across triplet types) with AGE GROUP (young vs. older) and DELAY (12, 24 hours or 1 week) as between-subject factors. The only significant effect was the main effect of AGE GROUP (F(1,123)=409.89, MSE=1784.08, $\eta_p^2=0.77, p<0.001$), reflecting longer RT's for the elderly group (537 ms) compared with the younger participants (381 ms). The main effect of DELAY and AGE GROUP x DELAY interaction did not approach significance (all p's>0.41). Thus, participants responded with similar overall reaction times in all delay conditions (see Figure 3.3.2c,d).

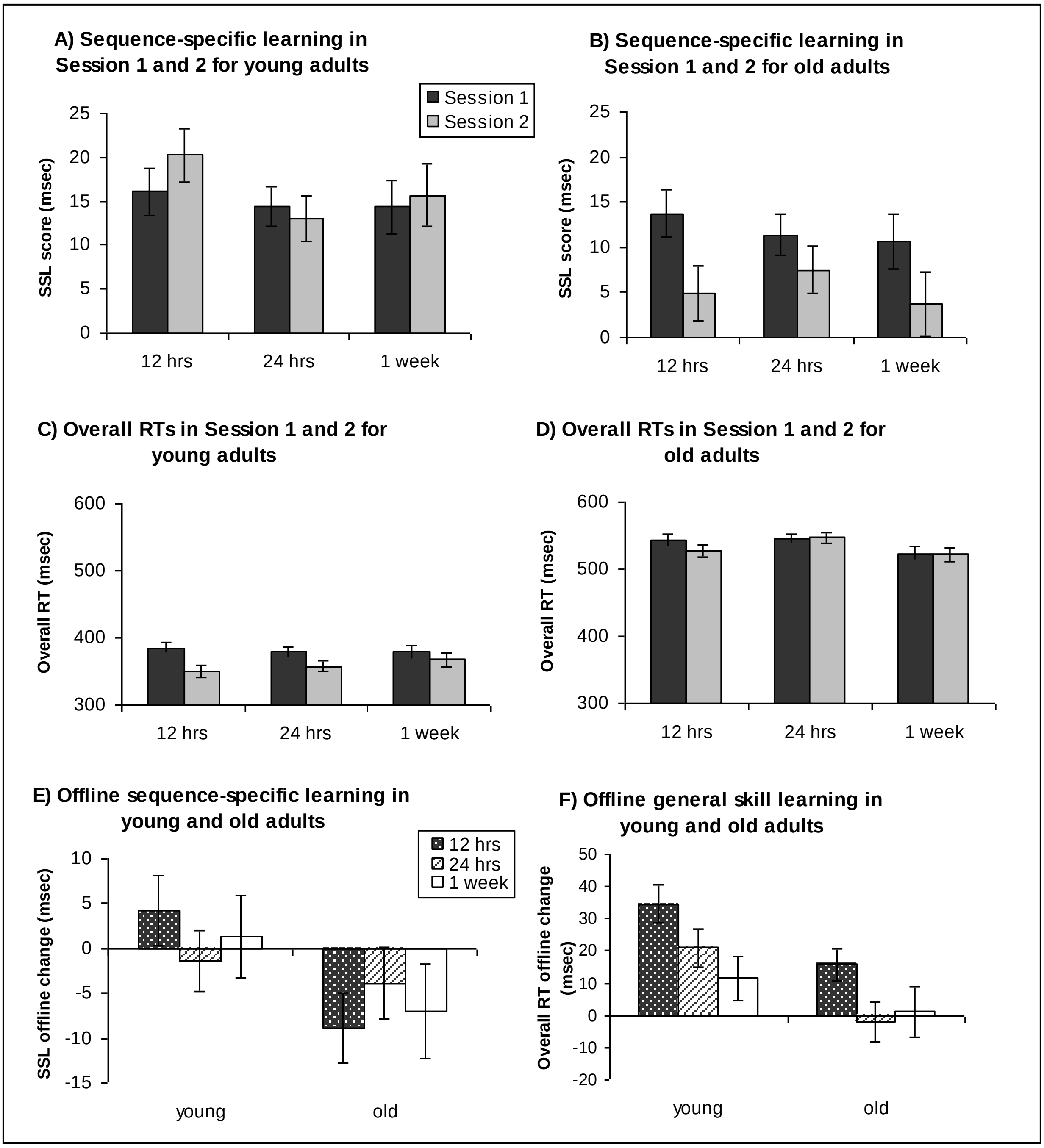

Figure 3.3.2: Sequence-specific learning (RT on Low- minus High-frequency triplets) at the end of Session 1 and at the beginning of Session 2 for young **(A)** and elderly groups **(B)**. All groups showed significant sequence-

specific learning by the end of Session 1. Overall RT's are also plotted at the end of Session 1 and at the beginning of Session 2 for young **(C)** and elderly groups **(D)**. Young participants were generally faster than the old ones. Regarding the offline sequence-specific learning (measured by the difference of sequence-specific learning (SSL) score at the end of Session 1 and the beginning of Session 2), young groups retained the previously acquired sequence-specific skill, while the elderly groups showed decrement in this skill compared to the young group. There were no differences across the 12, 24 hours and 1 week conditions **(E)**. Offline general skill learning (measured by the overall RT changes between the end of Session 1 and the beginning of Session 2) were obtained in all young groups and decreased gradually across delay conditions. Older adults showed offline improvement only after a 12-hours interval **(F)**. These groups responded significantly faster at the beginning of Session 2 compared to the end of Session 1, whereas elderly participants did not speed up after 24 hours or 1 week delay. Error bars indicate standard errors of mean (SEM).

Offline sequence-specific learning

To define the index of offline sequence-specific learning, we calculated the SSL learning score at the first epoch of Session 2 similarly to the learning score in Session 1 (Epoch 5). The greater this score at the beginning of the Session 2 compared to the end of Session 1, the larger the offline sequence-specific learning was. These two SSL learning scores were submitted to a Mixed-design ANOVA with SESSION (end of Session 1 vs. beginning of Session 2) as within-subject factor, and AGE GROUP (young vs. elder) and DELAY (12, 24 hours or 1 week) as between-subject factors. Thus, any offline change of sequence-specific learning would be revealed by main effects and/or interactions with SESSION.

The main effect of SESSION was not significant F(1,123)=2.28, MSE=178.4, $\eta_p^2=0.02$, p=0.13). However, the ANOVA revealed significant main effect of AGE GROUP F(1,123)=15.01, MSE=194.89, $\eta_p^2=0.11$, $p<0.001$) and significant SESSION x AGE GROUP interaction (F(1,123)=5.35, MSE=178.4, $\eta_p^2=0.04$, p=0.02), reflecting that age groups differed in offline sequence-specific learning. Sequence-specific knowledge decreased in the elderly groups (-6 ms) compared to the young, who retained the previously acquired skill (1 ms). There was no offline improvement of sequence-specific knowledge in either group.

Regarding the time course, there were no differences among delay conditions (neither the main effect, nor the interactions with DELAY was significant, p's >0.38), thus the consolidation of sequence-specific knowledge was not affected by the elapsed time between the learning and the testing session (see Figure 3.3.2e).

Offline general skill learning

Offline general skill learning was tested by comparing the overall RT's (collapsed across triplet types) between the last epoch of Session 1 and the first epoch of Session 2 (see Figure 3.3.2f). The greater the decrease from Session 1 to Session 2, the larger the offline general skill learning was. These two variables were submitted to a Mixed-design ANOVA with SESSION (end of Session 1 vs. beginning of Session 2) as within-subject factor, and AGE GROUP (young vs. older) and DELAY (12, 24 hours or 1 week) as between-subject factors. Similarly to previous analysis, any offline change of general skill would be revealed by main effects and/or interactions with SESSION.

This ANOVA revealed significant offline general skill improvement (indicated by the main effect of SESSION: F(1,123)=27.88, MSE=399.98, η_p^2=0.19, p<0.00001), participants responding faster at the beginning of Session 2 than at the end of Session 1. This offline improvement was larger for the young group than for the elderly participants (shown by the SESSION x AGE GROUP interaction: F(1,123)=11.45, MSE=399.98, η_p^2=0.09, p=0.001). In addition, the elapsed time between the two sessions influenced the improvement of general skill improvements as well (indicated by the SESSION x DELAY interaction: F(2,123)=5.29, MSE=399.98, η_p^2=0.08, p=0.006). Thus, participants' response speed improved more after the 12-hour than after the 24-hour (LSD post hoc test: p=0.007) or 1-week delay (p=0.006), whereas there was no difference between the 24-hour and 1-week delay conditions (p=0.64).

The subsequent paired-samples t-tests conducted separately for all age and delay groups revealed that the offline improvement of general skill was significant in all young groups (all p's<0.047), while in the elderly groups only the 12-hour delay led to offline enhancement (p=0.032). We also compared the performance of young and elderly groups in all conditions separately. Young adults showed larger offline improvement than the elderly participants in the 12-hour (t(44)=2.46, p=0.019) as well as in the 24-hour delay period (t(51)=2.96, p=0.006), while there was no significant difference between groups in the 1-week condition (t(28)=0.71, p=0.44).

Discussion

We studied the time course of implicit skill consolidation in young and elderly adults with probabilistic second-order regularity sequences (the ASRT task), which enabled us to separate general skill and sequence-specific learning. In the young adults, we found offline improvement of the general skill (overall RT) after the 12-, 24-hour and 1-week delay as well, with gradual decline among delays. The elderly adults showed offline improvement of general skill only after the 12-hour offline period and this improvement was weaker than that in the young group. Although the pattern in age groups is similar, these results suggest that the offline course of general skill learning may be affected by aging, since we did not find improvement either after 24-hour or 1-week delay in the elderly group. No offline improvement was found in sequence-specific learning in either age group with either the 12-, 24-hour or 1-week consolidation interval. Sequence-specific learning did not decrease significantly between sessions for young participants suggesting that sequence-specific knowledge was well consolidated in this group, whereas the older group showed weaker consolidation in all delay conditions compared to the young. So, according our results offline general skill learning is influenced both by the time course and aging, while the offline sequence learning is affected only by aging.

The significant offline general skill improvement after the 12-hour delay period is compatible with the results of Song et al. (2007b) and Nemeth et al. (2010). It is also possible that the improvement in overall RTs after the delay period reflects a release from fatigue rather than consolidation *per se*. However, studies that have included a fatigue control group (Spencer, Sunm, & Ivry, 2006; Walker et al., 2002) make this interpretation unlikely. The current results confirm those of Song et al. (Song et al., 2007b) and Nemeth et al. (2010) in finding no evidence of any offline improvement of sequence-specific performance and extend them to the 24-hour and 1 week consolidation period.

The offline general skill improvement after 12 hours in the elderly adults contrasts the findings of both Spencer et al. (2007) and Siengsukon et al. (2009b) who obtained no offline improvement in elderly adults. Due to the different paradigms used in the current and the two previous studies, it is difficult to identify the source of differences. We refer to the point that these previous studies did not distinguish between general skill and sequence-specific learning, and therefore the signal-to-noise ratio might be reduced making it difficult to detect the offline improvements for elderly participants.

The differences among the 12-, 24-hour and 1-week offline intervals suggest that the consolidation of general skill learning is time-dependent. In addition, older participants are more sensitive for this offline time course in that they showed no offline improvement even after 24-hour delay. These results are congruent with recent theories of motor skill consolidation (Press et al., 2005; Robertson et al., 2005; Shadmehr & Brashers-Krug, 1997; Walker, Brakefield, Hobson, et al., 2003) that claim that memory stabilization occurs during the first 5-6 hours after learning. The observed strong offline improvement after 12 hours may reflect this first stabilization process of memory traces, including the previously mentioned critical time period. The differences among 12-, 24-hour and 1-week consolidation intervals suggest that during new skill acquisition it could be important to place the training sessions closer to each other for optimal performance, with shorter intervals for elderly participants.

The current results as well as previous findings (Doyon, Korman, et al., 2009; Robertson, Pascual-Leone, & Press, 2004) are compatible with the notion that skill consolidation processes may be different and they could be profoundly dependent on the nature of task demand, such as on the relative proportion of general skill and sequence-specific learning requirements of the task. Given that these different components of learning are usually not separated in classical sequence learning tasks, offline improvements in such studies could be falsely attributed to sequence-specific learning itself. Nevertheless, in the current study consolidation of sequence-specific information was similar in the 12-, 24-hour and 1-week offline periods, with a decline for elderly compared to the young, independently of time course. These results suggest that stabilization of sequence-specific memory is a faster process, whereas offline changes of general skill are more influenced by a longer stretch of time.

On the functional level there are at least three mechanisms which may underlie the age-related decline in the consolidation of skill learning: 1) cognitive slowing may hinder elderly adults from having multiple representations simultaneously activated (see Salthouse's (1996) simultaneity theory); 2) associative binding deficits may cause impairment in making associations between multiple stimuli or stimulus features and binding these associations into long-term memory traces (Bennett et al., 2007; Harrison, Duggins, & Friston, 2006); 3) increased sensitivity to interference also can result weaker stabilization of representations (Park, Smith, Dudley, & Lafronza, 1989). On the neuronal level age-related decrement was observed both structurally and functionally in the basal ganglia (Chen et al., 2005; Erixon-Lindroth et al., 2005; Raz et al., 2005), that is involved in skill learning. Future studies are still needed to systematically examine the background mechanisms of age-related differences in skill consolidation.

Our findings are compatible with motor skill learning and consolidation models (D. A. Cohen et al., 2005; Doyon, Bellec, et al., 2009; Okihide Hikosaka et al., 1999; O. Hikosaka et al., 2002; Song, 2009; Walker, Brakefield, Hobson, et al., 2003), and draw attention to the fact that the consolidation is not a single process; instead there are multiple mechanisms in offline learning (general skill, sequence-specific processes), which are differently influenced by time course and by aging.

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3.4 The differential consolidation of perceptual and motor learning in skill acquisition[15]

Abstract

Implicit skill learning is an unconscious way of learning which underlies not only motor but also cognitive and social skills. This form of learning is based on both motor and perceptual information. Although many researches have investigated the perceptual and motor components of "online" skill learning, the effect of consolidation on perceptual and motor characteristics of skill learning has not been studied to our knowledge. In our research we used a sequence learning task to determine if consolidation had the same or different effect on the perceptual and the motor components of skill acquisition. We introduced a 12-hour (including or not including sleep) and a 24-hour (diurnal control) delay between the learning and the testing phase with AM-PM, PM-AM, AM-AM and PM-PM groups, in order to examine whether the offline period had differential effects on perceptual and motor learning. Although both perceptual and motor learning were significant in the testing phase, results showed that motor knowledge transfers more effectively than perceptual knowledge during the offline period, irrespective of whether sleep occurred or not and whether there was a 12- or 24-hour delay period between the learning and the testing phase. These results have important implications for the debate concerning perceptual/motor learning and the role of sleep in skill acquisition.

Keywords: consolidation, implicit skill learning, offline learning, perceptual-motor learning, sleep

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1. Introduction

Implicit skill learning occurs when information is acquired from an environment of complex stimuli without conscious access either to what was learned or to the fact that learning occurred (Reber, 1993). In everyday life, this learning mechanism is crucial for adapting to the environment and evaluating events. Implicit skill learning underlies not only motor but cognitive and social skills as well, it is therefore an important aspect of life from infancy to old age. Skill learning does not occur only during practice, in the so-called *online* periods, but also between practice periods, during the so-called *offline* periods. The process that occurs during the offline periods is referred to as consolidation which means stabilization of a memory trace after the initial acquisition. This process can result in increased resistance to interference or even improvement in performance following an offline period (Krakauer & Shadmehr, 2006; Nemeth, Janacsek, Londe, et al., 2010; Robertson, 2009; Song, 2009).

Most models of skill learning (Dennis & Cabeza, 2011; Doyon, Bellec, et al., 2009; Okihide Hikosaka et al., 1999; O. Hikosaka et al., 2002; Keele et al., 2003; Kincses et al., 2008) highlight the role of the basal ganglia and the cerebellum. One of the main debates in the field f skill learning is whether we rely on "our hands" or on "our eyes" (Deroost & E. Soetens, 2006; Keele et al., 2003; Mayr, 1996; Nemeth, Hallgato, Janacsek, Sandor, & Londe, 2009; Song et al., 2008; Ziessler & Nattkemper, 2001)? The goal of the present study is to determine if an offline period modifies the contribution of motor and perceptual components to implicit sequence learning. This issue is of particular interest because it deals with the question of whether sequence learning and consolidation are mediated by perceptual or by motor brain networks primarily (N. Deroost & E. Soetens, 2006; Goschke, 1998).

One of the most popular implicit learning tasks is the Serial Reaction Time (SRT) Task (M. J. Nissen & Bullemer, 1987) and its modification, the Alternating Serial Reaction Time (ASRT) Task (J. H. Howard, Jr. & Howard, 1997; Nemeth, Janacsek, Londe, et al., 2010). In the original version a stimulus appears at one of four possible locations on the screen, and subjects have to press the button corresponding to that location. Unbeknownst to them, the sequence of subsequent locations (and correspondingly, the sequence of the responses) follows a predetermined order. Without becoming aware of the sequence, subjects learn the regularity – and as they learn, they produce faster and more accurate responses. When the sequence is changed to a random series of stimuli, subjects become slower and less accurate in responding. In this paradigm, however, it is not clear what exactly the subjects learn: they might learn the sequence of the stimuli (*perceptual learning)*, the sequence of their own eye movements (*oculomotor learning)*, the sequence of response locations (*response-based learning*) or the sequence of given fingers' movements (*effector-based learning)* (Cohen, Ivry, & Keele, 1990; Remillard, 2003; Willingham, 1999).

In a SRT study Willingham (1999) used two conditions to examine the perceptual and the motor factors of learning. In one condition the stimulus–response mapping was changed in the transfer (test) phase that followed the learning phase, so that half of the subjects had to press the same sequence of keys as in the learning phase but saw new stimuli, whereas the other half had to press a different sequence of keys as in the learning phase but saw the same stimuli as before. Willingham (1999) found that transfer was shown only when the motor sequence was kept constant, but not when the perceptual sequence was constant. In a previous study, Nemeth et al. (Nemeth et al., 2009) compared the magnitude of perceptual and motor implicit sequence learning using a modification of the ASRT-task in a similar design. This task (ASRT-Race) contains second-order probabilistic sequences compared to classical SRT tasks that use deterministic sequences. ASRT-Race allows measuring "pure" sequence learning separate from general skill improvements, where sequence learning is reflected in the difference between the reaction times to more predictable events as opposed to less predictable ones. In addition, this task eliminates the possibility of oculomotor learning as stimuli always appear in the same central position on the screen. In contrast to Willingham's findings, Nemeth et al. (2009) demonstrated that not only motor, but perceptual learning of second-order probabilistic sequences is possible. Furthermore, Nemeth et al. (2009) showed that the two types of learning do not differ significantly in magnitude. The weakness of the above mentioned perceptual-motor studies (Deroost & E. Soetens, 2006; Mayr, 1996; Nemeth et al., 2009; Remillard, 2003, 2009; Song et al., 2008; Willingham, 1999) is that experiments were conducted in one session. Using only one session for measuring skill learning relates to short-term performance changes in behavior and not to more permanent changes associated with learning. Consequently, it is important to address the question of the role of offline periods in perceptual and motor skill learning.

Recent reviews indicate that whether offline improvements occur at all, and whether they are sleep-dependent, varies with factors such as awareness, the formation of contextual associations and type of information to be learned (Debas et al., 2010; Doyon, Korman, et al., 2009; Nemeth, Janacsek, Londe, et al., 2010; Robertson, 2009; Robertson, Pascual-Leone, & Press, 2004; Siengsukon & Boyd, 2008; Song, 2009; Song et al., 2007b). For example, Robertson (2009) argues that the consolidation of explicit (goal-directed) and implicit (movement-based) learning is differentially affected by sleep and wakefulness. In implicit learning when there is no declarative knowledge about the task, consolidation may occur during both wakefulness and sleep. In line with the predictions of this theory, recent SRT studies found similar consolidation of implicit skills during both sleep and wakefulness (Nemeth, Janacsek, Londe, et al., 2010; Robertson, Pascual-Leone, & Press, 2004; Song et al., 2007b).

Although many researches have investigated the perceptual and motor components of "online skill learning", to our knowledge, the effect of consolidation on perceptual and motor characteristics of skill acquisition has not been investigated so far (Deroost & E. Soetens, 2006; Mayr, 1996; Nemeth et al., 2009; Remillard, 2003, 2009; Song et al., 2008). In our study we used the ASRT-Race task (Nemeth et al., 2009) to examine the possible difference in the magnitude of motor and perceptual learning after a 12-hour and a 24-hour retention period. In addition, we also aimed at exploring the role of sleep in offline consolidation of these two factors of skill learning. Therefore a 12-hour delay was administered between the Learning Phase and Transfer Phase of the experiment, during which participants either had a sleep (night group) or they were awake (day group). If both groups acquire the same level of skill in the Learning Phase, any difference between them in the Transfer Phase will answer the question whether the perceptual or the motor component stabilizes more effectively during the offline period. In order to avoid time-of-day effect we also administered a 24-hour delay condition.

2. Methods

2.1. Participants

There were 102 individuals (students attending the University of Szeged) in the experiment (mean age= 22.34, SD= 3.82; 44 males, 58 females). None of them suffered from any developmental, psychiatric or neurological disorders. Participants were randomly assigned to the perceptual group or to the motor group. The perceptual and motor groups were further divided by the length of delay (12- or 24-hour delay) and by the daytime (morning first, AM-PM/AM-AM and evening first, PM-AM/PM-PM) (see Table 3.4.1). The eight experimental groups did not differ in their sleep quality (F(7,89)=0,98, p=0.45) measured by the Pittsburgh Sleep Quality Index (Due to data collection scheduling problems 5 out of 102 participants failed to administer this test). All individuals provided signed informed consent, and received no financial compensation for their participation.

Table 3.4.1. General data of participants

Condition	Delay	Daytime	Mean Age (SD)	N (Male/Female)
Perceptual	12-hour	Morning first (AM-PM)	20.82 (1.60)	11 (4/7)
		Evening first (PM-AM)	22.75 (3.74)	11 (7/4)
	24-hour	Morning first (AM-AM)	23.72 (5.66)	14 (4/10)
		Evening first (PM-PM)	21.63 (2.16)	14 (6/8)
Motor	12-hour	Morning first (AM-PM)	22.62 (3.98)	12 (8/4)
		Evening first (PM-AM)	22.00 (1.84)	11 (4/7)
	24-hour	Morning first (AM-AM)	20.40 (2.01)	12 (3/9)
		Evening first (PM-PM)	23.93 (5.48)	17 (8/9)

2.2. Procedure

All participants completed two sessions: a Learning Phase (Session 1) and a Transfer Phase (Session 2), separated by a 12-hour or a 24-hour delay (Figure 3.4.1). For the night groups, Session 1 was in the evening (between 7 and 9 pm), and Session 2 was in the morning (between 7 and 9 am), with the opposite arrangement for the day groups. Thus, the offline period of the night group contained sleep, while the day group was awake during the offline period (Figure 3.4.1). Although previous studies with similar tasks and experimental designs showed no time of day effect either on general reaction times or on learning measures (Nemeth, Janacsek, Londe, et al., 2010; Press et al., 2005; Robertson, Pascual-Leone, & Press, 2004; Song et al., 2007b), we administered a 24-hour delay condition. For the morning diurnal groups, both Session 1 and Session 2 were in the morning (between 7 and 9 am) and for the evening diurnal groups, both Session 1 and Session 2 took place in the evening (between 7 and 9 pm).

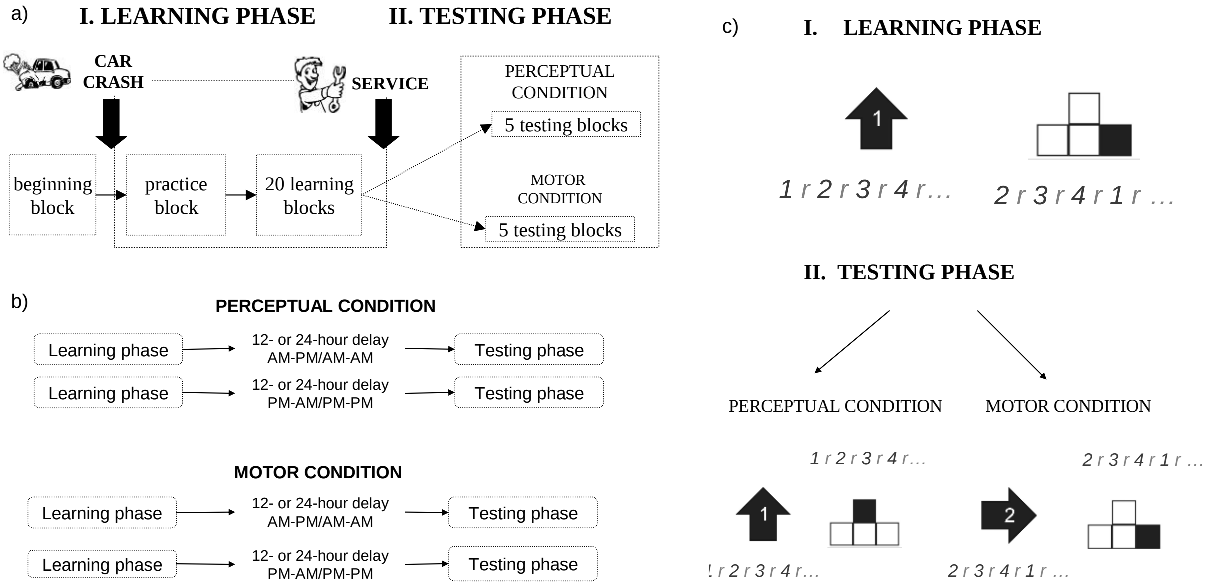

Figure 3.4.1. Design of the experiment. (a) All participants completed the ASRT-Race sequence learning task in two sessions. There were 20 learning blocks in Session 1 and 5 testing blocks in Session 2. (b) The two sessions were separated by either a 12-hour delay (in which participants had or had not slept) or a 24-hour delay. (c) In Session 2, half of the subjects were administered a new sequence which they had not seen before, but whose motor information corresponded to that of they had practiced in Session 1 (motor condition), while the other half of subjects were administered to the same perceptual information as in Session 1, but the pattern of motor responses changed due to the lack of mental rotation (perceptual condition).

2.3. Task

A modified version of the original ASRT (Howard and Howard, 1997) was used, the so-called ASRT-Race (Nemeth et al., 2009) in which the participants were instructed to drive an imaginary car on the road, as fast and as accurately as they can. The stimuli were the left, right, up and down arrows (5 cm long and 3 cm wide) appearing in the center of the screen, and representing the direction the car had to be steered. For example, when the subjects saw the right arrow, they had to press the right button on the keyboard to make a right turn with the car. All participants pressed the keys with their right hand.

Session 1 consisted of 22 blocks, starting with a block containing 85 random presses (excluded from data analysis), after which the individuals were told that there was a car crash and the steering wheel failed. Due to the defective steering wheel they had to mentally rotate the arrows appearing on the screen by 90°, and press the keyboard button designated to the rotated arrow, in order to maneuver the car in the right direction (Figure 3.4.1a). For instance, if they saw the up arrow on the screen they had to press the right arrow on the keyboard, if they saw the right arrow they had to press the down arrow button, and so on (Figure 3.4.1c). After the change in the instruction, there were 21 blocks, starting with 1 random block, in which participants could practice the new rules regarding the mental rotation, followed by 20 learning blocks (Learning phase). Each of the 20 learning blocks contained 85 key presses. The initial 5 stimuli were random (warm-up; excluded from data analysis), then an eight-element sequence alternated 10 times. Since the ASRT task is based on a non-adjacent sequence, random and sequence elements alternate one after the other. For example 2–R–3–R–1–R–4-R, where R represents random trials and the numbers represent the sequence-specific elements, implicating the arrows' direction (1-up, 2-right, 3-down, 4-left). The stimulus remained on the screen until the participant pressed the correct button. The next arrow appeared following a 120-ms delay (response to stimulus interval) after the subject's correct response. These parameters are consistent with the original task presented by Howard and Howard (1997). During this delay, a fixation cross was displayed on the screen. Participants were told to respond as fast and as accurately as they could.

Session 2 (Transfer Phase) took place either after a 12-hour or a 24-hour delay. The Transfer Phase consisted of 5 blocks. In this session participants were told that the car had been taken to a mechanic, and the steering wheel had been fixed, so they could use the answer keys corresponding to the arrows appearing on the screen (right button for right arrow, down button for down arrow, etc.). Half of the subjects participated in the motor condition, while the other half was assigned to the perceptual condition. Subjects in the motor condition were administered a new sequence which they had not seen before, but whose motor information corresponded to that of they had practiced in Session 1, while subjects in the perceptual condition were administered to the same perceptual information as in Session 1, but the pattern of motor responses changed due to the lack of mental rotation (Figure 3.4.1c). Thus, while in Session 1 all subjects performed the same task, in Session 2 they were divided into two groups (perceptual vs. motor). The difference between the two groups allowed us to separate the motor and the perceptual information of the sequence previously learnt by the subjects so this way we could determine whether the perceptual and the motor component had the same or different effects on learning. All the stimuli were displayed in the center of the screen in order to exclude the possible oculomotor aspect of learning. After Session 2, we administered a short questionnaire regarding the participants' possible explicit knowledge about the task (Song et al., 2007). In keeping with other probabilistic SRT studies (L Jiménez et al., 2006; Nemeth, Janacsek, Londe, et al., 2010; Song et al., 2007b), none of them reported noticing the sequences.

2.4. Data analysis

Since the core structure of the tasks was the same as in the original ASRT, we followed the same procedures in our analysis (Howard and Howard, 1997; Nemeth et al., 2010b). As there is a fixed sequence in the ASRT-Race with alternating random elements (also known as non-adjacent sequence) (Remillard, 2008), for example 2–R–3–R–1–R–4-R, some triplets or runs of three events occur more frequently than others. For instance, following the illustration above, triplets such as 2**_3**, 3**_1**, 1**_4**, 4**_2** (where "_" indicates the middle element of the triplet) can occur more often, because the third element (bold numbers) could be derived from the sequence, or could also be a random element. In contrast, triplets such as 4**_1**, 4**_4** would occur infrequently, because in this case the third element could only be random. Following previous studies, we refer to the former as high-frequency triplets and the latter as low-frequency triplets. Because of this difference in frequencies of certain triplets, after observing two stimuli, a certain third stimulus can be expected with 62,5% of probability (for example, 22*3* is five times more probable than 22*1* or 22*2* or 22*4*). In our analysis, we determined for every stimulus if it was the more probable or the less probable continuation for the previous trials (see Figure 3.4.2). Participants are faster at the probable stimuli than at the less probable ones, revealing sequence learning in the ASRT paradigm (Howard et al., 2004; Song et al., 2007).

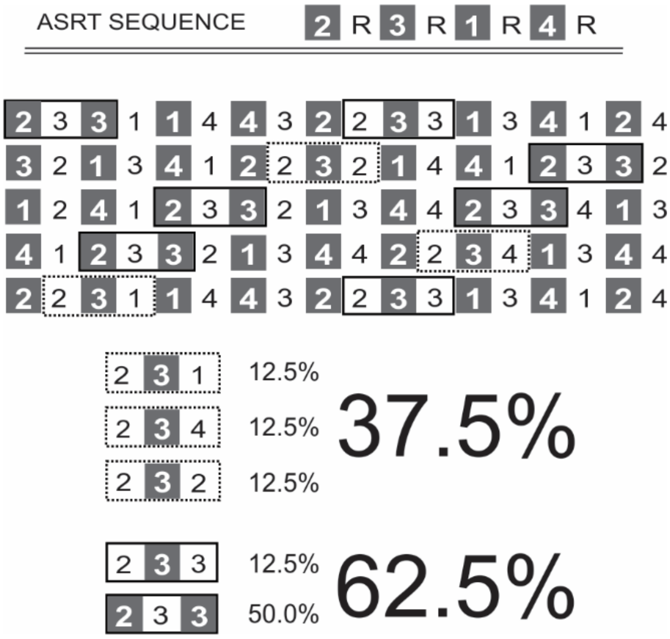

Figure 3.4.2. In a typical ASRT sequence, there are more frequent (high frequency) triplets and less frequent (low frequency) triplets. In other words, if we know what were the last two elements of the sequence (in this case *2-3-?*), there is a 62.5% probability of a certain element as continuation, and only 12.5% probability of all of the other elements.

Similar to prior investigations, two kinds of low-frequency triplets were excluded from the analysis; trills (e.g. 121, 434) and repetitions (e.g. 111, 222). These triplets are low frequency for all individuals, and people often show pre-existing response tendencies to them. By eliminating these triplets, we can assure that any high versus low frequency differences are due to learning, and not pre-existing tendencies (D. V. Howard et al., 2004; Nemeth et al., 2009; Nemeth, Janacsek, Londe, et al., 2010).

Since the accuracy of the participants was very high (average over 94.92% in all groups, in all phases), our analysis focused on RT data. For statistical analysis, median RTs were calculated for correct responses only, for each subject for every five blocks, both for the low-frequency and high-frequency elements.

To define the index for *Sequence Learning Effect (SLE)* (Nemeth & Janacsek, 2011; Nemeth, Janacsek, Londe, et al., 2010; Song et al., 2007b; Song et al., 2009), we calculated the RT difference between the low and high frequency triplets separately in the Learning Phase (Session 1) and in the Transfer Phase (Session 2) for every five blocks. As we subtracted RT-s of high frequency triplets from those of low frequency triplets, SLE was a positive number only if sequence learning occurred, a larger value indicating a stronger effect.

3. Results

3.1. Learning in Session 1

To be able to investigate the effect of transfer after 12- and 24-hour delay, learning in Session 1 must be similar in the groups. From this point of view, the end of Session 1 is crucial (Nemeth & Janacsek, 2011; Nemeth, Janacsek, Londe, et al., 2010; Press et al., 2005; Song et al., 2007b). Therefore, we analyzed the SLE of the last five blocks of the Learning Phase for every group. Univariate ANOVA was conducted with CONDITION (perceptual vs. motor), DAYTIME (morning first vs. evening first groups) and DELAY (12- and 24-hour) as between-subject factors. ANOVA revealed significant sequence learning ($F(1,94)=32.31$, $p<0.001$) which is inferred from the test whether the overall mean is different from zero (Mean SLE=11.16 ms). There were no other significant main effects or interactions involving CONDITION, DAYTIME and DELAY (all p's>0.32), thus these between-subject factors had no significant effect on sequence learning.

3.2. Transfer of Sequence Learning Effect from Session 1 to Session 2

To determine whether the performance in Session 2 declined, improved, or was constant in relationship to the end of Session 1, we subtracted the SLE score of the last five blocks of the Learning Phase from the SLE score of the Transfer Phase (Transfer-SLE). As the groups were similar in SLE at the end of Session 1 (Learning Phase), any difference among groups in Transfer-SLE could be attributed to the differential effects of consolidation. We conducted a univariate ANOVA for this Transfer-SLE score with CONDITION (perceptual vs. motor), DAYTIME (morning first vs. evening first groups) and DELAY (12- and 24-hour) as between-subject factors. ANOVA revealed a main effect of CONDITION (F(1,94)=4.92, p=0.029), the motor group showing larger SLE than the perceptual group (Figure 3.4.3). ANOVA showed no significant main effect or interaction with DAYTIME (all p's>0.45), suggesting that the AM-PM, PM-AM, AM-AM and PM-PM groups did not differ in their SLE. In addition, main effect and interactions with DELAY were not significant either (all p's>0.25), suggesting that 12- and 24-hour delay groups performed at a similar level.

Thus, the only significant effect in the ANOVA was the main effect of CONDITION, suggesting differential consolidation of perceptual and motor groups with better consolidation for motor group, irrespectively of the delay or daytime. Despite this difference in consolidation, SLE in Session 2 was significantly different from zero for both the perceptual and motor groups (one-sample t-tests for SLE scores: t(49)=5.25, p<0.001 and t(51)=8.72, p<0.001 respectively). Thus, in spite of the weaker consolidation in the perceptual group, they still showed significant SLE in the Transfer Phase (Session 2). For detailed descriptive statistics see Appendix 1.

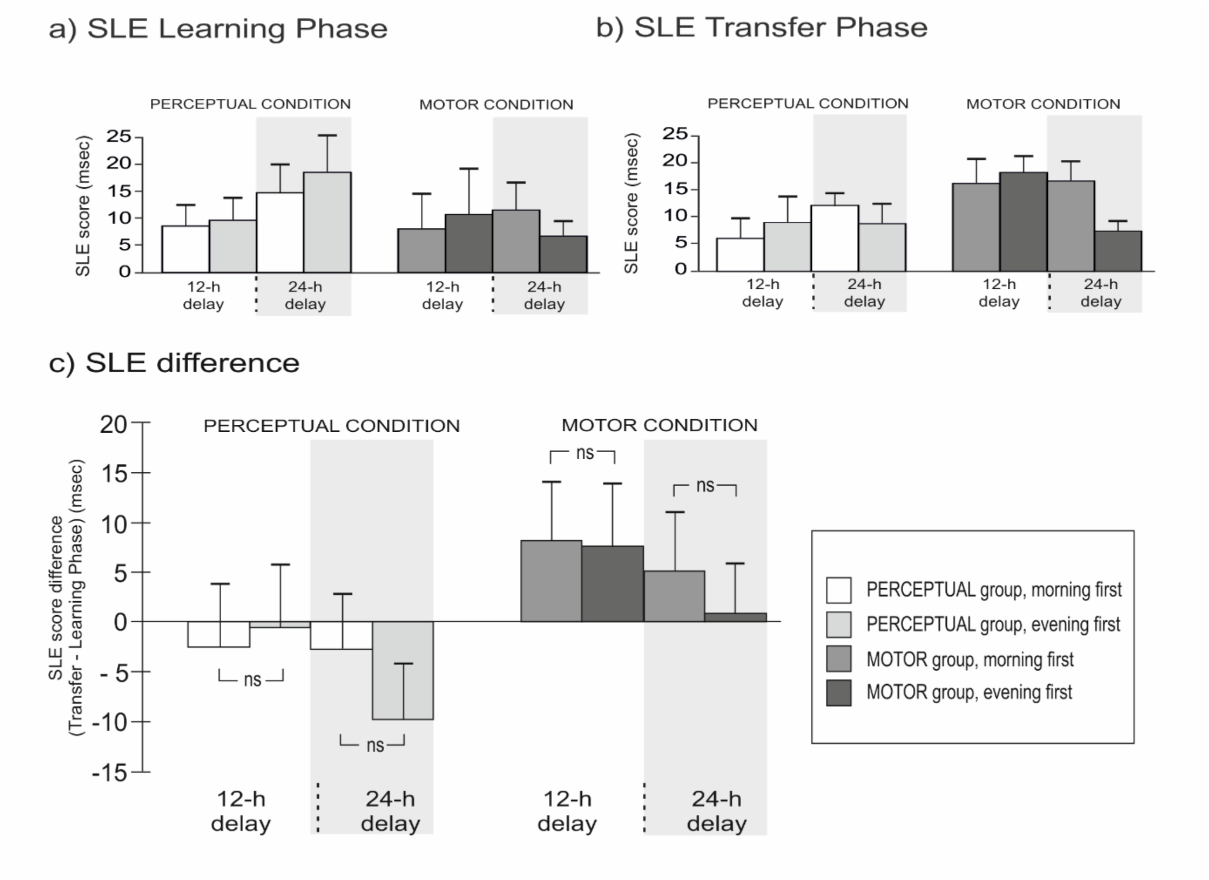

Figure 3.4.3. A) SLE score (Sequence Learning Effect) of each experimental group in the last 5 blocks of the Learning Phase. B) SLE score of each experimental group in the Transfer Phase (Session 2). C) Difference between SLE scores of the 5 blocks of Transfer phase and the last 5 blocks of Learning phase (Transfer SLE score). The perceptual groups showed weaker transfer effect than the motor groups both after 12 and 24 hours. Error bars indicate Standard Error of Mean.

3.3. Transfer or new motor learning in Perceptual Group?

In order to find out whether the significant learning effect in Transfer Phase (Session 2) is due to new motor learning in the perceptual condition we investigated the learning effect at the beginning of the Learning Phase (Session 1 – the first two sequence blocks) and in the Transfer Phase (Session 2 – Block 1-2) separately. We calculated SLE scores for the first 2 blocks of Session 1 and Session 2. We submitted these scores to a one-sample t-test separately for Session 1 and Session 2. If we can show a significant learning effect in Session 1 – Block 1-2, the learning is very fast; and the results in Session 2 can be due to new motor learning. However, we found no significant learning effect in Session 1 – Block 1-2 in the perceptual group (one-sample t-test for SLE-score: t(49)=-1.069, p=0.291, Mean SLE=-9.27). In contrast we found a significant learning effect in Session 2 – Block 1-2 (one-sample t-test for SLE-score: t(49)=3.523, p=0.001, Mean SLE=8.33). Hence it is likely that the learning effect in

Session 2 (Transfer Phase) is attributable to preserved perceptual learning rather than a new motor learning. We found the same pattern in the motor condition (one-sample t-test for SLE-score in Session 1 – Block 1-2: t(51)=0.3, p=0.765, Mean SLE=3.89; Session 2 – Block 1-2: t(51)=5.087, p<0.001, Mean SLE=14.77). For detailed descriptive statistics see Appendix 2.

4. Discussion

Our study investigated the role of 12-hour and 24-hour delay on perceptual and motor components of implicit skill learning, while eliminating oculomotor learning. In this way we connect two debates together: 1) one on the relative importance of perceptual and motor learning 2) the other on the effect of sleep on skill acquisition. We used the same method as Nemeth et al.'s study (2009), except that in our research there was a 12-hour (during which participants either had sleep or they were awake) or a 24-hour (diurnal) offline period between the Learning and the Transfer Phase. We found significant sequence learning in the Learning Phase. After the 12-hour and the 24-hour offline period we found significant learning effect in both the perceptual and the motor conditions, however transfer in the motor condition was more effective compared to the perceptual condition. We did not find any sleep-effect on sequence learning in either condition.

The weaker consolidation of perceptual learning is in agreement with the results of Deroost and Soetens (2006) and Willingham (1999), who found no evidence of perceptual learning, only under specific conditions. According to previous studies, perceptual learning only takes place when the structure of the sequence is simple, but in case of deterministic sequences with second-order dependencies and probabilistic sequences with first-order dependencies perceptual learning is not or only weakly present (N. Deroost & E. Soetens, 2006; Mayr, 1996; Remillard, 2003). Also, previous studies found perceptual learning in explicit conditions (Russeler & Rosler, 2000), and when a motor sequence was learnt concurrently (Mayr, 1996). In our study participants had no conscious awareness at all of the structure of the sequence, as the ASRT task uses probabilistic sequences with second-order dependencies. The only condition that met Deroost's (2006) criteria is that in the Learning Phase participants learnt the perceptual and motor components concurrently. Compared to Nemeth et al. (2009) who found similar magnitudes of perceptual and motor learning immediately after the Learning Phase, we found a weaker perceptual learning effect in the Transfer phase both after a 12-hour and a 24-hour delay. As the only difference was the 12-hour or the 24-hour delay, we can suppose that the differences between the results of the two studies can be related to the consolidation period. Thus, this one criterion (i.e. participants in the Learning Phase learnt the perceptual and motor components concurrently) can be enough for finding significant perceptual learning immediately after the Learning Phase (B. Meier & Cock, 2010; Nemeth et al., 2009; Weiermann, Cock, & Meier, 2010), however, it might result in weaker consolidation after the delay period. To put the puzzle together, based on the present study we can propose that the consolidation period has a differential effect on motor and perceptual components of learning, so that in the Transfer Phase the motor learning effect is larger than the perceptual one.

Song et al. (2008), Nemeth et al. (2009) and the present study are similar in the nature of the sequence structure and the implicitness of the task. Furthermore, the present study and the study of Nemeth et al. (2009) also eliminated the possibility of oculomotor learning. As we focused only on the perceptual and motor learning while controlling the oculomotor learning, the role of *response-based learning* and *effector-based learning* remained unclear (A. Cohen et al., 1990; Remillard, 2003; Willingham, 1999). This way, the exact nature of the underlying mechanism still needs to be investigated.

In addition to the question of perceptual and motor components of learning, our study has relevance for the sleep debate in skill consolidation (Debas et al., 2010; Doyon, Korman, et al., 2009; Gerván & Kovács, 2007; A Karni, 1994; Robertson, 2009; Song, 2009; Stickgold & Walker, 2005; Walker et al., 2002). As pointed out by Robertson (2009) and supported by Song et al. (2007b) and Nemeth et al. (2010), we found that sleep does not support sequence learning. In addition, sleep has no different role in the consolidation of motor and perceptual factors of implicit sequence learning. A plausible explanation can be that in the probabilistic sequence learning task used in this study, besides primary sensory and motor brain regions, sub-cortical structures and cerebellum are more involved (Doyon, 2008; Okihide Hikosaka et al., 1999; O. Hikosaka et al., 2002), opposed to the more basic finger tapping tasks where sleep-dependent improvement was usually found (Walker et al., 2002).

To conclude, in spite of the 12-hour or the 24-hour offline period we found a significant perceptual and motor learning effect in the Transfer Phase, however the transfer of the motor knowledge was more robust, irrespective of whether sleep occurred in the consolidation period or not. These results have important implications for the perceptual/motor and also for the sleep debate in skill learning in the following ways: 1) previous experiments in this field included only one session which can reveal short-term performance changes in behavior. Consequently, it is important to use more sessions with many hours (even a day) delay between sessions for measuring permanent changes in neural plasticity. 2) Sleep has no contribution to this type of learning. However, further investigations need to explore more deeply conditions (including nature of sequence, awareness, perceptual/motor learning) in which sleep has a significant role in skill learning. 3) The retention period itself (regardless of sleep) has a modifying effect on the consolidation of perceptual/motor knowledge and the underlying brain networks.

Appendices

Appendix 1. Means and standard deviations (SD) for sequence learning effects (SLE) at the end of the Learning Phase, at the beginning of the Transfer Phase. SLE-change indicates the difference in sequence learning effects between the two sessions.

Condition	**Delay**	**Daytime**	**N**	**SLE (Learning Phase)**		**SLE (Transfer Phase)**		**SLE-change (Transfer – Learning)**	
				Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**
Perceptual	12-hour	Morning-first	11	8.59	12.57	6.09	12.06	-2.50	17.45
		Evening-first	11	9.68	13.27	9.14	15.68	-0.55	18.47
	24-hour	Morning-first	14	14.82	19.39	12.11	8.70	-2.71	16.75
		Evening-first	14	18.64	25.42	8.86	13.64	-9.79	28.29
	Total		50	13.39	18.87	9.22	12.41	-4.17	20.78
Motor	12-hour	Morning-first	12	8.13	22.51	16.29	15.20	8.17	19.14
		Evening-first	11	10.73	27.96	18.36	9.03	7.64	27.58
	24-hour	Morning-first	12	11.63	18.27	16.67	12.18	5.04	24.64
		Evening-first	17	6.68	11.63	7.56	6.79	0.88	12.63
	Total		52	9.01	19.53	13.96	11.54	4.95	20.46
Total			102	11.16	19.24	11.41	14.45	0.48	21.02

Appendix 2. Means and standard deviations (SDs) for the first two sequence blocks of the Learning and Transfer Phase for perceptual and motor condition.

Condition	**Phase**	**Mean**	**SD**
Perceptual (N= 50)	Learning	-9.27	61.34
	Transfer	8.33	16.72
Motor (N=52)	Learning	3.89	93.46
	Transfer	14.77	20.94

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3.5 Evidence for one-year consolidation of implicit probabilistic learning[16]

Abstract

Statistical learning is a robust mechanism of the brain that enables the extraction of environmental patterns, which is crucial in perceptual and cognitive domains. However, the dynamical change of processes underlying long-term statistical memory formation has not been tested in an appropriately controlled design. Here we show that a memory trace acquired by statistical learning is resistant to inference as well as to forgetting after one year. Participants performed a statistical learning task and were retested one year later without further practice. The acquired statistical knowledge was resistant to interference, since after one year, participants showed similar memory performance on the previously practiced statistical structure after being tested with a new statistical structure. At the same time, the underlying learning processes became less flexible, since participants could not learn the new statistical structure per se. These results could be key to understand the computational underpinnings of long-term memory.

Keywords: implicit learning, interference, long-term memory, predictive processing, statistical learning

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[16] Published in Kóbor A., Takács, Á., Janacsek, K., & Nemeth, D. (under review). Stable but less flexible representation of statistical regularities: Evidence for resistance to interference after one year *Scientific Reports*

Introduction

Statistical learning is a fundamental mechanism of the brain which extracts and represents regularities of our environment. It is crucial in perception (Fiser & Aslin, 2002; Orban et al., 2008; Teinonen, Fellman, Näätänen, Alku, & Huotilainen, 2009; Winkler, Denham, & Nelken, 2009; Yang & Purves, 2003), associative learning (Turk-Browne, Scholl, Johnson, & Chun, 2010), predictive processing (Bar, 2007; Turk-Browne et al., 2010; Winkler et al., 2009), and acquisition of perceptual, motor, cognitive, and social skills; thus, statistical learning underlies many day-to-day activities during the entire lifespan (Kaufman et al., 2010; Saffran et al., 1996; Ullman, 2004). Moreover, statistical learning could be considered as the basis of language acquisition (M. C. Frank, Tenenbaum, & Gibson, 2013; Saffran et al., 1996). Despite the extensive research on this field, the strong implicit assumption that statistical learning leads to persistent memory has not yet been empirically tested in a carefully controlled experimental design, and the dynamics of those mechanisms underlying consolidation have remained unclear. Here we show direct evidence for one-year retention and resistance to interference of a memory trace that was acquired by statistical learning in humans.

An important challenge of neuroscience is to unravel how brain plasticity leads to memory formation, what are the temporal dynamics of memory formation, and how long-term memory traces are retained. Learning-related plastic changes in the brain take place not only during sessions of practice, in the so-called “online” periods, but also between sessions of practice, during the so-called “offline” periods (Lisa Genzel & Robertson, 2015). Offline processing of learnt information is referred to as consolidation, which pertains to the stabilization of memory traces after their initial acquisition (Krakauer & Shadmehr, 2006; Beat Meier & Cock, 2014; Nemeth & Janacsek, 2011; Robertson, 2009; Robertson, Pascual-Leone, & Miall, 2004; Song et al., 2007b).

Although some previous studies investigated the long-term retention of different perceptual-motor skills in humans using various tasks (Ammons et al., 1958; Fleishman & Parker, 1962; O Hikosaka et al., 2002; Willingham & Dumas, 1997), only the study of Romano, Howard, and Howard (2010) examined the long-term stability of *statistical learning*, but even these findings were limited in validity. Although the retention of statistical memory was found after one year in a small sample of perceptual-motor skill experts and older non-experts, the authors did not investigate whether statistical memory was resistant to new, interfering information. In fact, the general effect of interference on statistical learning has not been investigated within an extended time period. In this way, only the *retention* of memory traces could have been measured rather than their *consolidation*, which could not unravel the core processes underlying long-term memory formation. Therefore, the aim of the current study is twofold as follows. First, we explore the nature of those dynamic processes that underpin the long-term consolidation of statistical regularities by introducing interfering sequences in the course of learning. Second, we provide a valid replication of the study conducted by Romano et al. (2010) on a larger, homogeneous sample and show clear empirical evidence that statistical learning leads to persistent and immutable memory traces that are resistant to forgetting over a longer stretch of time. This combined approach enables to examine the flexibility of learning processes and the robustness of representations related to statistical regularities, since the change in performance measured on the previously practiced and the new, interfering sequence could be quantified.

In the current study, healthy young adults performed a statistical learning task and they were retested one year later without further practice between the two tests. Statistical learning was induced by a perceptual-motor four-choice reaction time task that, unknown to the participant, included a temporal/serial regularity between non-adjacent trials. By reason of this structure, the task can mimic the complexity of an incoming stream of information from the environment. During the testing phases, this task, along with its original version, was also administered with a different underlying structure to test the susceptibility of the acquired statistical knowledge to interference.

Material and methods

Participants

Forty-six healthy young adults participated in the three-session-long study. Retention of the acquired statistical knowledge (i.e., statistical memory) over the one-year period can only be assessed for those participants who exhibited significant statistical memory before the one-year delay. By including these participants, we exclude the possibility of learning the statistical regularities only after the one-year delay. Twenty-nine of the 46 participants met this criterion; therefore, one-year retention was assessed in the *final sample of 29 adults* (mean age = 19.93 years, *SD* = 1.98 years; mean years of education = 13.36, *SD* = 1.72 years; 28 females). The criterion for showing significant statistical memory is specified in the Statistical Analysis section.

All participants in the final sample as well as in the original sample had normal or corrected-to-normal vision and none of them reported a history of any neurological and/or psychiatric condition. Prior to their inclusion in the study, participants provided informed consent to the procedure as approved by the research ethics committee of Eötvös Loránd

University, Budapest, Hungary. The study was conducted in accordance with the Declaration of Helsinki and participants received course credits for taking part in the experiment.

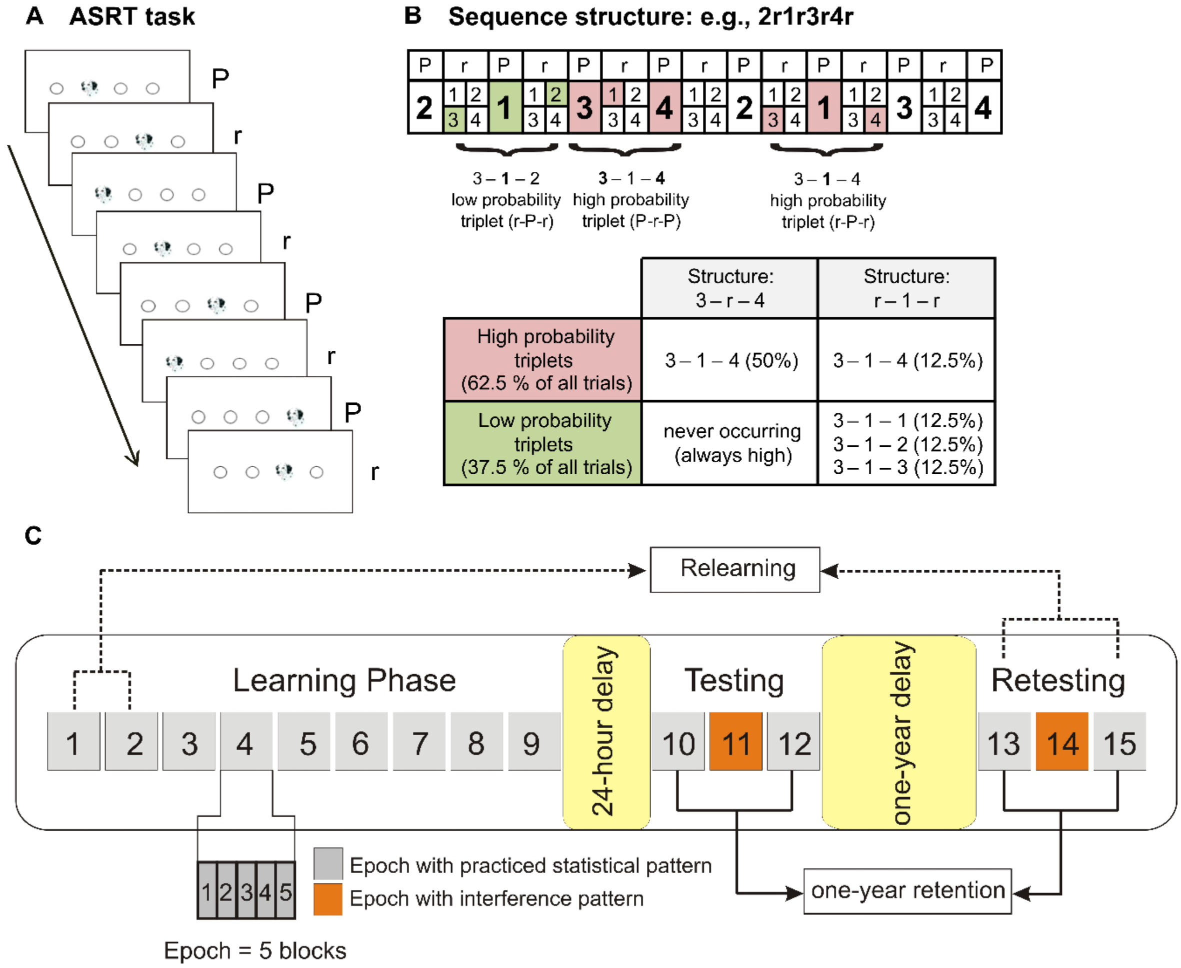
Task

The Alternating Serial Reaction Time (ASRT) task was used to induce statistical learning (Song et al., 2007b). In this task, a stimulus (a dog's head) appeared in one of four horizontally arranged empty circles on the screen (Nemeth, Janacsek, & Fiser, 2013). Participants were instructed to press a corresponding key (Y, C, B, or M on the Hungarian keyboard) as quickly and accurately as possible when the stimulus occurred. Unbeknownst to the participants, the presentation of stimuli followed an eight-element sequence, within which predetermined (P) and random (r) elements alternated with each other (e.g., 2 – *r* – 1 – *r* – 3 – *r* – 4 – *r*; where numbers denote the four locations on the screen from left to right, and *r'*s denote randomly chosen locations out of the four possible ones; see Fig. 3.5.1A).

The alternating sequence in the ASRT task makes some patterns of three consecutive elements (henceforth referred to as triplets) more frequent than others. In the example above, 2X1, 1X3, 3X4, and 4X2 (X indicates the middle element of the triplet) occurred often since the third elements could have either been a predefined or a random element (see Fig. 3.5.1B). At the same time, 1X2 and 4X3 occurred less frequently since the third element could have only been random. The former triplet types were labeled as "high-probability" triplets while the latter types were labeled as "low-probability" triplets (Nemeth, Janacsek, Polner, et al., 2013). The third element of a high-probability triplet was more predictable from the first element of the triplet than in the case of low-probability triplets. For instance, in the example shown on Fig. 3.5.1B, Position 3 as the first element of a triplet is more likely (62.5%) to be followed by Position 4 as the third element, than either Position 1, 2, or 3 (12.5%, each). In accordance with this principle, *each item* was categorized as either the third element of a high- or a low-probability triplet, and the accuracy and reaction time (RT) of the response to this item were compared between the two categories.

This task overcomes a common challenge of the field in that it allows us to separate pure statistical learning from general skill improvements. Statistical learning is defined as faster and more accurate responses to high conditional probability events compared to that to low conditional probability ones (Fig. 3.5.1B) (Song et al., 2007b). In contrast, general skill improvements refer to the speed-up and changes in accuracy, which are independent of the conditional probabilities of the events. These improvements reflect more efficient visuomotor and motor-motor coordination due to practice(Hallgato et al., 2013).

In our study, participants were unaware of the underlying conditional probability structure of the stimulus sequence, and they did not even know that they were in a learning situation. Thus an implicit, non-conscious form of learning was tested (Cleeremans & Dienes, 2008; Reber, 1989). This has also been confirmed using a short questionnaire and the Inclusion-Exclusion Task (see section Testing the implicitness of the acquired statistical knowledge in the Supplementary Material).



	Structure: 3 – r – 4	Structure: r – 1 – r
High probability triplets (62.5 % of all trials)	3 – 1 – 4 (50%)	3 – 1 – 4 (12.5%)
Low probability triplets (37.5 % of all trials)	never occurring (always high)	3 – 1 – 1 (12.5%) 3 – 1 – 2 (12.5%) 3 – 1 – 3 (12.5%)

Figure 3.5.1. Design of the experiment. (A) In the Alternating Serial Reaction Time (ASRT) task, a stimulus appeared in one of four horizontally arranged empty circles on the screen. The presentation of stimuli followed an eight-element sequence, within which predetermined (P) and random (r) elements alternated with each other. (B) The alternating sequence in the ASRT task makes some patterns of three consecutive elements (triplets) more frequent than others. (C) The ASRT task was administered in three sessions. During the Learning Phase, the ASRT task included 9 epochs. Both the Testing and the Retesting Phase included only 3 epochs with identical structure. The middle epoch of both of these sessions (Epoch 11 and 14) served as interference with the repeating sequence being different from the one appearing in all other epochs.

Procedure

The ASRT task was administered in three sessions. During the Learning Phase, the ASRT task included nine epochs, each containing five blocks (45 blocks in total), with 85 trials (stimuli) in each block. In each block, the eight-element sequence repeated 10 times after five warm-up trials consisting only of random stimuli. Both the Testing and the Retesting Phase included only three epochs (i.e., a total of 15 blocks of stimuli, each). The middle epoch (5 blocks) of both of these sessions (Epoch 11 and 14) served as interference with the repeating sequence being different from the one appearing in all other epochs. Thus the two tests had identical structure (Fig. 3.5.1C). Participants were not told about the change in the underlying sequence during interference blocks. In addition, they were unaware of the fact that they were going to practice the same task with the same interfering sequence one year later.

Statistical Analyses

To increase statistical power, we analyzed epochs of five blocks instead of single blocks. Therefore, the Learning Phase consisted of nine epochs, while the Testing and Retesting Phases consisted of three epochs. Epochs are labeled consecutively (1, 2,…, 15) in the remainder of paper (see Fig. 3.5.1C). Mean accuracy (ratio of correct responses) and median RT only for correct responses were determined for each participant and epoch, separately for high- and low-probability triplets. Learning scores in the Learning Phase and memory scores in the Testing and Retesting Phases were then calculated as the difference between triplet types in RT (RT for low-probability triplets minus RT for high-probability triplets) and accuracy (accuracy for high-probability triplets minus accuracy for low-probability triplets). Greater score in both measures indicates larger statistical learning/memory. To evaluate statistical learning and retention of the acquired statistical knowledge, we conducted repeated measures analyses of variance (ANOVAs) and paired-samples *t*-tests. Greenhouse-Geisser epsilon (ε) correction was used when necessary. Original *df* values and corrected *p* values (if applicable) are reported together with partial eta-squared (η_p^2) as the measure of effect size. Analyses and results concerning accuracy are only reported in the Analysis of accuracy data section of the Supplementary Material; here we focus on RT measures.

In a special case, to increase the sensitivity of our measures to temporal changes, median RT were determined for blocks instead of epochs. Namely, only those participants were included in the final sample, who showed significant statistical memory in the Testing Phase. This was evaluated blockwise in the following way. (1) We considered only those 10 blocks of the Testing Phase in which we presented the same repeating sequence to participants as in the Learning Phase. These blocks are henceforth referred to as *non-interference* blocks or epochs (the cluster of five blocks; Fig. 3.5.1C). (2) In the Testing Phase, median RT for correct responses was calculated for each participant, block, and triplet type. (3) We calculated the statistical memory score (difference in RTs for low- vs. high-probability triplets) for each block in the Testing Phase. (4) One-sample *t*-tests against zero were run on these scores for each participant to confirm whether they showed any significant statistical memory. A deviation from zero was regarded as significant if the *p*-value was less the .050. Twenty-nine participants met this criterion (mean score = 18.68 ms, *SD* = 7.96 ms).

As the focus of the current study is on the retention of statistical memory, we performed Bayesian paired-samples *t*-tests and calculated the Bayes Factor (BF) for the relevant comparisons (see the Results section below). The BF is a statistical technique that helps conclude whether the collected data favors the null-hypothesis (H_0) or the alternative hypothesis (H_1); thus, the BF could be considered as a weight of evidence provided by the data (Wagenmakers, Wetzels, Borsboom, & van der Maas, 2011). It is an effective mathematical approach in consolidation studies where it is expected that the acquired evidence supports H_0 rather than H_1 (Dienes, 2011, 2014; Wagenmakers, 2007). In this case, H_0 is the lack of difference between the two means, and H_1 states that the two means of memory scores differ. BFs were calculated using the JASP (version 0.6, see Love et al.; Rouder, Speckman, Sun, Morey, & Iverson, 2009). Here we report BF_{01} values. According to Wagenmakers et al. (2011), BF_{01} values between 1 and 3 indicate anecdotal evidence for H_0, while values between 3 and 10 indicate substantial evidence for H_0. Conversely, while values between 1/3 and 1 indicate anecdotal evidence for H_1, values between 1/10 and 1/3 indicate substantial evidence for H_1. If the BF is below 1/10, 1/30, or 1/100, it indicates strong, very strong, or extreme evidence for H_1, respectively. Values around one do not support either H_0 or H_1.

Results

The prerequisite of memory consolidation

Before memory consolidation can be assessed, significant statistical learning needs to occur preceding the long delay period (i.e., during the Learning and Testing Phases). Statistical learning during the Learning Phase was tested with a two-way repeated measures ANOVA for RT with TRIPLET (high- vs. low-probability) and EPOCH (1–9) as within-subjects factors. The ANOVA revealed significant statistical learning and general skill improvements (significant main effects of TRIPLET, $F(1, 28) = 96.71, p < .001, \eta_p^2 = .774$, and EPOCH, $F(8, 224) = 72.08, \varepsilon = .303, p < .001, \eta_p^2 = .720$). Participants were increasingly faster on high- than on low-probability triplets as the task progressed (TRIPLET*EPOCH interaction, $F(8, 224) = 7.51$, $\varepsilon = .617$, $p < .001$, $\eta_p^2 = .212$; see Fig. 3.5.2).

Thus, there was evidence for both statistical learning and general skill improvements during the Learning Phase. Significant statistical learning and general skill improvement before the one-year delay also took place during the Testing Phase, as this was the criterion for participants to be included in the final sample.

Resistance to forgetting

To test the one-year retention of the learned statistical contingencies, we first checked whether there is any change in statistical memory performance between the non-interference epochs of the Testing and Retesting Phases (i.e., resistance to forgetting; see Fig. 3.5.1C). An ANOVA was conducted for RT with SESSION (Testing vs. Retesting), TRIPLET (high- vs. low-probability), and EPOCH (10, 12 vs. 13, 15) as within-subjects factors. We found substantial evidence for retained statistical memory after one-year delay (non-significant SESSION*TRIPLET interaction, $F(1, 28) = 0.08$, $p = .774$, $\eta_p^2 = .003$; $BF_{01} = 4.873$) with similar memory scores during Testing and Retesting Phases (see Fig. 3.5.3).

Irrespective of the retention of statistical memory, the same ANOVA revealed partially decreased general skills over the one-year delay. Participants were significantly slower in the Retesting Phase compared to the Testing Phase (significant main effect of SESSION: $F(1, 28) = 24.32$, $p < .001$, $\eta_p^2 = .465$; $BF_{01} = 0.001$). These results suggest that while statistical learning leads to persistent memory representations over the one-year delay, some aspects of general skills undergo forgetting over this period.

The effect of the interference sequence

Testing Phase. The effect of interference sequence on statistical memory was evaluated in three steps. *First*, if statistical memory about the initial sequence was still flexible during the Testing Phase, there should be significant statistical learning on the interference epoch, as well, in which the underlying sequence is unfamiliar to participants. *Second*, if statistical learning occurred in the previously practiced, non-interference epochs, then weaker performance in the interference epoch compared to the non-interference epochs (Epoch 11 vs. Epochs 10 and 12 in the Testing Phase) should be expected. *Third*, if statistical memory acquired during previous practice was robust against interference, performance on the non-interference epoch (Epoch 12) *following* the interference epoch (Epoch 11) should be the same or even better than that on the non-interference epoch (Epoch 10) *preceding* the interference epoch.

First, we found statistical learning on the interference epoch as the statistical memory score for RT significantly differed from zero (M = 4.40 ms, $t(28) = 3.00$, $p = .006$, BF_{01} = 0.133). Second, a TRIPLET (high- vs. low-probability) by EPOCH (10, 11, and 12) two-way repeated measures ANOVA on the RT measure was conducted to test statistical learning throughout all epochs of the Testing Phase. The ANOVA revealed significant TRIPLET*EPOCH interaction (see Fig. 3.5.2) indicating smaller statistical learning in the interference epoch than in non-interference epochs ($M_{\text{interference}}$ = 4.40 ms vs. $M_{\text{non-interference}}$ = 18.58 ms; $t(28) = 7.60$, $p < .001$, $BF_{01} = 2.030*10^{-6}$). Third, we compared statistical memory performance in the two non-interference epochs of the Testing Phase, and found resistance to interference since there was no significant difference between Epoch 12 and Epoch 10 (M_{Epoch12} = 19.72 ms vs. M_{Epoch10} = 17.43 ms; $t(28) = -1.16$, $p = .257$, BF_{01} = 2.764).

In summary, the significant statistical learning during interference is evidence that participants were still able to acquire new statistical information in the Testing Phase. In addition, we found weaker performance in the interference epoch compared to non-interference epochs, and efficient resistance to interference.

Retesting Phase. To examine the effect of interference after one year has elapsed, we followed those three analysis steps described above in relation to the Testing Phase. First, we *did not* find statistical learning on the interference epoch as the statistical memory score for RT did not significantly differ from zero (M = 1.24 ms, $t(28) = 0.76$, $p = .454$, BF_{01} = 3.888). Second, we conducted a TRIPLET (high- vs. low-probability) by EPOCH (13, 14, and 15) two-way repeated measures ANOVA for RT in the Retesting Phase, similarly to the analysis in the Testing Phase. Statistical learning was smaller in the interference epoch than in non-interference epochs (Fig. 3.5.2; $M_{\text{interference}}$ = 1.24 ms vs. $M_{\text{non-interference}}$ = 18.09 ms; $t(28) = 7.69$, $p < .001$, $BF_{01} = 1.661*10^{-6}$). Third, we compared statistical memory performance in the two non-interference epochs of the Retesting Phase, and found resistance to interference since there was no significant difference between Epoch 15 and Epoch 13 (M_{Epoch15} = 20.12 ms vs. M_{Epoch13} = 16.09 ms; $t(28) = -1.57$, $p = .127$, BF_{01} = 1.687).

In summary, the lack of substantial evidence for statistical learning during interference suggests that participants did not acquire new statistical information in the Retesting Phase, after one year had elapsed. At the same time, they showed weaker performance in the interference epoch than in non-interference ones, as well as efficient resistance to interference in the Retesting Phase.

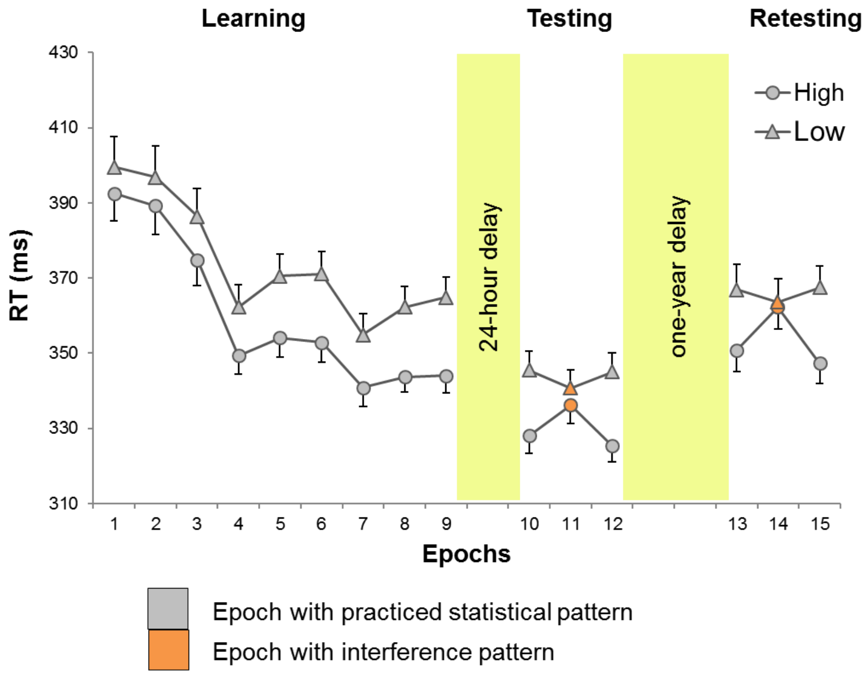


Figure 3.5.2. Temporal dynamics of statistical learning across epochs and sessions. Group-average (*N* = 29) RT values for correct responses as a function of the epoch (1–15) and trial type (high- vs. low-probability triplets) are presented. Error bars denote standard error of mean.

Comparing the effect of interference sequence across Testing and Retesting Phases. In two steps, we examined whether the acquired statistical knowledge was resistant to interference across the Testing and Retesting Phases in a similar level. *First*, we assessed whether the difference in memory scores between the non-interference and interference epochs in the Retesting Phase (Epoch 13 and 15 vs. Epoch 14) was at a similar level as that in the Testing Phase (Epoch 10 and 12 vs. Epoch 11). We found similar *level of interference* in the Testing and Retesting Phases ($M_{\text{Testing Phase}} = 14.18$ ms vs. $M_{\text{Retesting Phase}} = 16.85$ ms, $t(28) = -1.17$, $p = .251$; $BF_{01} = 2.72$) (see Fig. 3.5.3).

Second, we tested whether the difference in statistical memory scores between Epoch 12 and 10 vs. the difference in statistical memory scores between Epoch 15 and 13 were similar. We found substantial evidence for the same *level of resistance to interference* in the Testing and Retesting Phases ($M_{\text{Epoch12-10}} = 2.29$ ms vs. $M_{\text{Epoch15-13}} = 4.05$ ms; $t(28) = -0.55$, $p = .589$, $BF_{01} = 4.414$). Thus, the interference epoch did not deteriorate performance in the in the following non-interference epoch in either of the phases.

In sum, the level of interference on statistical memory and the level of its resistance to interference were similar in the Testing and Retesting Phases.

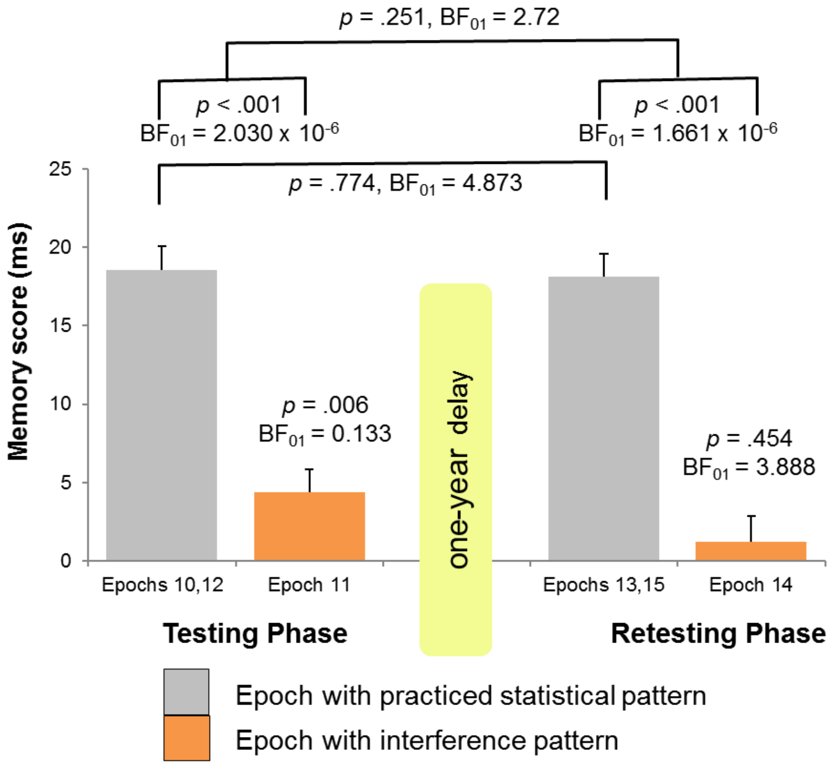


Fig. 3.5.3. Retention of the acquired statistical knowledge. Group-average of memory scores measured by RT for the non-interference (Epoch 10,12 and Epoch 13,15) and interference epochs (Epoch 11 and Epoch 14) of the Testing and the Retesting Phase, respectively. While significant statistical learning was found on the interference epoch in the Testing Phase, there was no significant learning on the interference epoch in the Retesting Phase. Error bars denote standard error of mean.

Testing relearning the statistical regularities after one-year delay

To rule out the possibility that the one-year retention of statistical memory is due to relearning in the Retesting Phase, additional ANOVAs were run with the SESSION (Learning vs. Retesting Phase), TRIPLET (high- vs. low-probability), and EPOCH (1 and 2 vs. 13 and 15) as within-subject factors (Fig. 3.5.1C). The significant SESSION*TRIPLET interaction ($F(1, 28) = 25.34$, $p < .001$, $\eta_p^2 = .475$) showed larger statistical memory after the one-year delay than at the beginning of the Learning Phase ($M_{13,15} = 18.10$ ms vs. $M_{1,2} = 7.26$; $BF_{01} = 0.001$). In sum, the learning measure confirms that participants did not relearn the task after the one-year delay, which provides further evidence for the one-year retention of statistical memory.

Discussion

In this study we have shown clear evidence for the long-term consolidation of statistical memory in a carefully controlled experimental design, which involved interference manipulation. Moreover, we have highlighted how the flexibility of learning processes underlying statistical memory changed over a longer stretch of time. Statistical memory scores were similar after 24 hours and one year, irrespective of the type of learning measure (i.e., accuracy or RT, see Supplementary Material). Participants successfully acquired and stabilized the previously learned material, and after 24 hours, their neurocognitive system underlying learning remained flexible to learn new, interfering information to which they were only briefly exposed. After one year has elapsed, although it seems that knowledge about the primarily learnt statistical structure remained stable, the system underlying learning became more rigid during the long delay, since after a brief exposure, participants could not learn the new statistical structure that was also presented to them a year before. The addition of this new statistical structure affected statistical learning performance on the primarily practiced sequence in a comparable degree after 24 hours and one year, which indicates that the acquired statistical knowledge remained persistent over time (Robertson, Pascual-Leone, & Miall, 2004).

Previous studies have shown that some aspects of skill acquisition are based on probabilistic perception and probabilistic learning (Fiser & Aslin, 2001; Fiser, Berkes, Orbán, & Lengyel, 2010; Orban et al., 2008; Saffran et al., 1996). However, it has not been proven that statistical learning alone can lead to long-lasting representations, because in other studies and observations, several confounding factors were present: For instance, practice after the initial acquisition of statistical regularities together with the intervention of higher-order cognitive processes (as a result of the person intending to learn the given skill) could lead to reactivation, reconsolidation, and substantial alteration of the original memory traces. Therefore, our study took five possible confounds of consolidation into account. First, we controlled for short-term (i.e., 24-hour) consolidation of the acquired knowledge of conditional probabilities by inserting a Testing Phase and analyzing one-year retention only in those participants who showed stable statistical memory in it. Second, we used identical design in the Testing and the Retesting Phase by inserting an interference epoch in both sessions in order to test both resistance to forgetting and resistance to interference after one year. Third, we ruled out the possibility of relearning by showing better performance after the one-year period than at the very beginning of the Learning Phase. Fourth, there was no intervening practice during the one-year period, minimizing the possibility of reactivation of the acquired statistical memory during this time window. Fifth, learning was implicit because participants were unaware of the learning situation, the statistical structure of the stimulus stream, as well as of the fact that they will be tested one year later, controlling for any confounding effects of explicit strategy use during memory encoding and consolidation. Moreover, our results are supported by Bayesian statistics besides general linear models (cf. Materials and Methods). Therefore, in regard to the applied rigorous methodology, results of the present study further extend the findings of Romano et al. (2010) about the long-term retention of statistical regularities.

The retention of statistical knowledge after the long delay extends the findings of (Nemeth & Janacsek, 2011) and Beat Meier and Cock (2014), who found comparable retention of sequential memory across 12-hr, 24-hr, and one-week delay intervals. It is conceivable that those processes related specifically to the *retention* of statistical knowledge do not change already after 12-hour delay (see also Nemeth, Janacsek, Londe, et al., 2010; Press et al., 2005), which is also in line with our finding that the acquired statistical knowledge was equally robust to interference both after 24 hours and one year.

In our design general skill improvements refer to general speed-up, independent of the statistical structure of the task, reflecting more general learning mechanisms. Previous studies (Beat Meier & Cock, 2014; Nemeth & Janacsek, 2011) found improved general skills both after 24 hours and one week compared to the end of the training session, but the degree of improvement did not differ between the two delay intervals. Moreover, retained general skills were also found after one year (Romano et al., 2010). In the present study, general skills were retained over the one-year period measured by accuracy (see section Resistance to forgetting in the Supplementary Material) but were decreased measured by RT (i.e., slower overall RT). It is possible that the lack of practice on the ASRT task might have affected only the speed and not the precision of visoumotor coordination, which resulted in slower RTs after the one-year delay. This finding suggests that some aspects of general skills undergo forgetting over one-year if no further practice is intervened. However, overall accuracy and RT were decreased after one year as compared to the *beginning* of the first session, suggesting that the general skill was retained at least in some degree (cf. Romano et al., 2010). The latter evidence also corroborates our previous statement about the implausibility of relearning the ASRT task after the offline period. Nevertheless, future studies need to disentangle how these aspects of general skills consolidate over a longer stretch of time (cf. O Hikosaka et al., 2002). In the neuroscience of skill learning, a long-standing issue is that general skill learning mechanisms are heavily intertwined with statistical or sequence-specific learning, which hinders the possibility to draw conclusions about statistical learning itself. The strength of our study is that it could separate pure statistical learning from these mechanisms and could directly investigate the one-year retention of pure statistical learning.

Our results suggesting that the representation of the original statistical structure is immune to interference and the underlying system is only flexible to learn a new statistical structure within a limited time interval extend the study of Gebhart, Aslin, and Newport (2009). In an auditory statistical learning task where two different statistical structures (artificial languages) determined the presented stimuli, Gebhart et al. (2009) showed that participants could learn only the first structure of speech streams if no explicit information was given about the change in structure during the task or the second structure was not presented for a longer duration. Accordingly, it is conceivable that more blocks of the interference sequence in our design could have increased the chance to relearn the interference sequence after one year elapsed, and the primacy effect (see also e.g., Billig & Carlyon, 2016; da Estrela & Byers-Heinlein, 2015; Junge, Scholl, & Chun, 2007; Yu & Zhao, 2015) of the first statistical pattern could be disrupted. However, as the Gebhart et al. (2009) study showed, learning a new structure did not attenuate performance on the original structure, which was also the case in our study after the 24-hour delay (i.e., resistance to interference). Nevertheless, it still remains unclear whether far more practice on the interference sequence could cause performance deterioration on the non-interference sequence, or the different representations of the two statistical structures could be maintained and the same time and individuals could flexibly switch between them. An advantage of having a more stable or elaborated primary structure is that the underlying cognitive/perceptual mechanisms remain sensitive to this structure later, even if the organism has to learn other statistical regularities in the meantime (Gebhart et al., 2009). The long-term impact of the primarily acquired statistical structure and its predictive power have also been demonstrated in the perception of the auditory environment (Mullens et al., 2014; Todd, Provost, & Cooper, 2011) and in processing native and non-native phonetic features of word stress (Honbolygó & Csépe, 2013) as indicated by event-related brain potentials (e.g., the mismatch negativity).

Importantly, we found that statistical knowledge was somewhat rigid or inflexible as learning did not occur on the interference epoch after one year, which supports that the mechanism of statistical learning is related to habit formation (e.g., Dolan & Dayan, 2013; Neal, Wood, Labrecque, & Lally, 2012). Usually, habits are complex sequential behaviors that are present is most activities performed repeatedly in an automatized manner during daily life (Cleeremans et al., 1998; Montague, Dolan, Friston, & Dayan, 2012). Although habits ease everyday activities by enabling them to be performed without effort, potentially destructive habits (smoking, alcohol use, gambling) could also develop. Therefore, the present findings might contribute to better understand the difficulty of changing maladaptive routines and behaviors, which also exist in clinical syndromes (Everitt & Robbins, 2005).

Results of the present study are also compatible with the strong impression coming from daily experience that skills, such as speaking a language or playing tennis, once acquired, are persistent throughout life. Our findings, therefore, provide new possibilities for the study of language (Saffran et al., 1996), visual (Orban et al., 2008) and sensorimotor (Kording & Wolpert, 2004) skill acquisition by showing that statistical learning mechanisms are sufficient to explain the formation of persistent memory representations, thus provide a basis of long-term memory. Moreover, by giving insight to the dynamic change of underlying learning processes, we could provide an experimentally well-controlled design and a possible explanatory framework for other studies investigating the long-term retention of statistical structures embedded in other perceptual/cognitive domains under more natural circumstances. For instance, on a small sample of participants, M. C. Frank et al. (2013) found retention of large-scale artificial languages even after three years, although participants were only exposed to these languages for 10 days without directly paying attention to the presented chunks of languages. The authors claimed this was an evidence that statistical learning skills related to speech segmentation could be applied to the lexicons of natural languages. A simple paradigm such as the ASRT task might be used over an even longer time period to test the upper bound of the retention of statistical knowledge, and to obtain a clearer insight to the characteristics of processes determining consolidation in such a large-scale as language acquisition (see also Morgan-Short, Finger, Grey, & Ullman, 2012).

Taken together, the present study shows that probabilistic mechanisms are not only present in perception and learning but also that their results remain stable over longer periods of time. Specifically, we demonstrated that statistical knowledge was resistant to interference and also to forgetting after one year. Our experimental design enabled to test how the flexibility of neurocognitive processes underlying learning changed over this time period: We showed that although the statistical knowledge remained stable, processes mediating statistical learning lost some of their flexibility of acquiring similar but essentially new regularity between the elements of the incoming stream of information. In the long run, these results can help to build a better computational framework (Fiser et al., 2010) of systems-level brain mechanisms that underlie learning and memory.

Acknowledgements

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4. DISCUSSION[17]

The aim of the thesis was to explore the learning and consolidation phase of implicitly learned sequences. In the learning phase, we discovered important factors that can influence this fundamental learning mechanism (see Table 4.1).

Table 4.1. Summary table of the results from the implicit learning studies

Chapter	Factors	Goals and questions	Results
2.1	Childhood development and aging	Which time is the best to acquire new skills? Determine age-related changes across the human lifespan in probabilistic sequence learning	Before 12 years of age, the learning performance is better than in later ages. Performance gradual declines with age. The question of z-score in developmental studies.
2.2	Age and awareness	What are the differences in the developmental curves of explicit and implicit sequence learning?	Explicit cues can prevent the decline in learning performance after 12-13 years of age. Different learning processes and different learning scores have been invented, discovered.
2.3	Control processes	How can we boost implicit learning? Determine the competition between control processes and implicit learning	Hypnosis can boost implicit learning via inducing less reliance on control processes.
2.4	Executive functions	Can weaker executive functions lead to better implicit learning? Determine the role of executive functions in implicit learning	Weaker executive functions lead to better implicit learning performance.
2.5	Perceptual and motor	How motor and perceptual factors contribute to implicit sequence learning? Determine the perceptual and motor factors of learning	Perceptual and motor factors are comparably relevant in learning.

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[17] Based on Janacsek, K., & Nemeth, D. (2012). Predicting the future: from implicit learning to consolidation. *International Journal of Psychophysiology*, *83*(2), 213-221.

2.6	Secondary task	Can a secondary task disturb implicit sequence learning?	In a dual-task situation, the secondary task cannot disrupt implicit learning only in the case of sentence processing.
2.7	Working memory	What is the role of working memory in implicit learning?	Implicit sequence learning seems to be independent of working memory measured by classical working memory span tasks.
2.8	Atypical development	How atypical development such as autism affect implicit learning?	We found intact implicit learning in autism. Implicit learning seems to be a very robust learning mechanism.
2.9	Mild Cognitive Impairment	Can Mild Cognitive Impairment disturb implicit learning? What is the role of the hippocampus in implicit learning?	We invented a new method to measure different processes underlying implicit sequence learning. We found impaired learning in MCI, with weaker performance in the first part of the learning blocks (hippocampus-dependent processes).

The "competition" framework can explain several results presented in this thesis, specifically those of the two developmental studies (Chapter 2.1 and 2.2; Janacsek et al., 2012; Nemeth et al. 2013), as well as those of the hypnosis study (Chapter 2.3; Nemeth et al., 2013) and the negative correlations found in the alcohol study (Chapter 2.4; Virag et al., 2015). These findings indicate that the weaker the frontal lobe functions and/or the weaker the connectivity of the frontal lobe with other brain regions, the better the implicit and statistical learning performance is.

These results and the suggested framework are in line with previous studies that showed a negative or competitive relationship between frontal functions and implicit learning processes (Filoteo et al., 2010, Poldrack et al., 2001). Several developmental studies can also be explained by the 'competition' framework. Munakata and colleagues (2012, 2014) further added to this question by presenting the developmental aspects of frontal lobe functions and executive functions, and showing that as one matures, the two functions become more and more dependent on the same cognitive resources. These results are in line with the results of Janacsek et al. (2012) in that they also showed a similar pattern: maturation of the frontal lobe (and cognitive control) negatively affects the implicit learning performance.

A better insight of the competition between frontal lobe-related executive functions and fronto-striatal networks linked to implicit learning can contribute to the understanding of the development of implicit learning mechanisms, which could easily become a valid tool for therapies and cognitive rehabilitation programs.

Factors influencing consolidation

The second aim of the thesis was to investigate the factors that can significantly affect the consolidation of implicit learned sequences (Table 4.2).

Table 4.2. Summary table of the results from the consolidation studies

Chapter	Factors	Goals and questions	Result
3.1	Aging and sleep	What is the role of sleep in the consolidation of implicit learning? Does aging affect sleep-dependent consolidation?	Sleep has no effect on the consolidation of implicitly learned sequences, neither in young nor in older adults.
3.2	Aging and length of the offline period	Which length of the offline period is optimal for consolidation: 12h, 24h or 1 week? Is there any interaction between the effects of aging and length of the offline period on consolidation?	Regarding sequence-specific learning, no offline improvement was found at either consolidation interval. Regarding aging, sequences-specific knowledge decreased in the elderly group independently of the delay.
3.3	Sleep disorder	Can Sleep disorder disrupt the consolidation of implicit learning?	We found intact sequence-specific consolidation in patients with sleep disorder. In contrast, consolidation of general skills was weaker in the patient group compared to the controls.
3.4	Sleep and perceptual-motor factors	Does sleep have a critical role in the consolidation of perceptual and motor factors of implicit learning? Determine the perceptual and motor factors in the consolidation of implicit learning	We found no sleep effect in implicit sequence learning, irrespectively of the condition (perceptual or motor).
3.5	Length of the offline period	Is implicitly learned information retained after one year? Is there evidence for resistance to interference after one year?	We found no forgetting in implicit sequence learning after a one-year delay period, suggesting robust consolidation processes.

Length of the offline period

Previous consolidation studies examined only a shorter stretch of time, so the question remained of what happens in consolidation after 12 or more than 12 hours. The second part of the thesis focused on these issues.

In the study of Chapter 3.2 we investigated the time course of implicit sequence learning by comparing the performance after 12-, 24-hour, and 1-week delays from the initial learning session (Nemeth & Janacsek, 2011). We focused on the consolidation of implicit sequence-specific learning, and separately, general skill learning between young and elderly adults. The aim of the study was to determine a time point in a longer stretch of time at which improvement can still be observed in consolidation, and analyze its possible age-related differences. In the young adults, the researchers found offline improvement of the general skill after all three delay periods, with a gradual decline among delays. Although no offline improvement was found in sequence-specific learning with any of the consolidation intervals, it did not decrease significantly between sessions for young participants, suggesting that sequence-specific knowledge consolidated well. Thus, according to these results, offline general skill learning is influenced by the time course. In contrast, offline sequence-specific learning is not affected by the length of the offline period, since the consolidation of sequential knowledge had already occurred after a 12-hour delay, and did not differ from the 24-hour and 1-week delay conditions.

These results are congruent with recent theories of consolidation (Press et al., 2005; Robertson et al., 2005; Shadmehr & Brashers-Krug, 1997; Shadmehr & Holcomb, 1997; Walker, Brakefield, Hobson, et al., 2003), which claim that memory stabilization occurs during the first 5-6 hours after learning. The strong offline improvement of general skill that was observed after 12 hours may reflect this first stabilization process of memory traces, including the previously mentioned critical time period (Nemeth & Janacsek, 2011). In addition, consolidation of sequence-specific information was similar in the 12-, 24-hour, and 1-week offline periods, independently of time course. These results suggest that the stabilization of sequence-specific memory is a faster process because it had already occurred after 12 hours and did not differ from the other delay conditions. In contrast, in the case of general skill learning, further changes were observed after longer time intervals (e.g., 24-hour and 1-week delays) compared to the 12-hour delay condition (Nemeth & Janacsek, 2011). In recent studies (Kobor, Janacsek, Takacs, & Nemeth, submitted; Romano Bergstrom et al., 2012)(Chapter 3.5), retention of the sequence-specific knowledge was found after a full year, suggesting that sequence knowledge without further practice is stable even after much longer periods.

Perceptual and motor factors of sequence learning

Another major debate in the field of sequence learning is whether we rely on “our hands” or on “our eyes” during learning (Keele et al., 2003; F. Kemény & Lukács, 2011; Mayr, 1996; Nemeth et al., 2009; Song et al., 2008; Ziessler & Nattkemper, 2001) (see Chapter 2.5 and 3.4). In the classical sequence learning paradigms, such as the SRT and ASRT tasks, exactly what the participants learn is not clear: They might learn the sequence of the stimuli (perceptual learning), the sequence of their own eye movements (oculomotor learning), the sequence of response locations (response-based learning), or the sequence of given finger movements (effector-based learning) (A. Cohen et al., 1990; Remillard, 2003; Willingham, 1999). These factors determine not only the online learning process but also the consolidation of sequence knowledge.

In an SRT study, Willingham (1999) used two conditions to examine the perceptual and the motor factors of learning. In one condition, the stimulus–response mapping was changed in the transfer (test) phase that followed the learning phase, so that half of the participants had to press the same sequence of keys as in the learning phase but saw new stimuli (motor condition), whereas the other half had to press a different sequence of keys as in the learning phase but saw the same stimuli as before (perceptual condition). Willingham (1999) found that transfer was shown only when the motor sequence was kept constant, and not when the perceptual sequence was constant. In Chapter 2.5, Nemeth et al. (2009) compared the magnitude of perceptual and motor components of implicit sequence learning using a modification of the ASRT-task in a similar design.

In the ASRT-Race task, the stimuli were the left, right, up, and down arrows, which appeared in the center of the screen (minimizing oculomotor movements). In the learning phase, participants had to mentally rotate the arrows by 90 degrees to the right, and press the button corresponding to this rotated arrow. In the transfer phase, the stimulus-response mapping changed and participants no longer had to rotate the arrows (rather, they had to press the left button when seeing the left arrow). Half of the participants were assigned to the perceptual and the other half to the motor condition. In the perceptual condition, the perceptual sequence was the same, but the motor sequence (key presses) changed compared to the previously practiced sequence. Conversely, key presses followed the previously learned sequence and the perceptual information (the sequence of the stimuli displayed on the screen) changed in the motor condition. The goal of comparing the participants' performance between these two conditions was to determine whether the contribution of perceptual and motor component was the same as or different from the learning (for more details see Chapter 2.5, Nemeth et al., 2009). This task involves second-order probabilistic sequences, whereas classical SRT tasks use deterministic sequences. ASRT-Race also allows "pure" sequence learning to be measured separately from general skill improvements, where sequence learning is reflected in the difference between the reaction times to more as opposed to less predictable events. In addition, this task eliminates the possibility of oculomotor learning, as stimuli always appear in the same central position on the screen. In contrast to Willingham's findings, Nemeth et al. (2009) demonstrated that not only motor but also perceptual learning of second-order probabilistic sequences is possible. Furthermore, Nemeth et al. (2009) showed that the two types of learning do not differ significantly in magnitude.

Although several studies have investigated the perceptual and motor components of online sequence learning (N. Deroost & E. Soetens, 2006; Mayr, 1996; Nemeth et al., 2009; Remillard, 2003, 2009; Song et al., 2008), to our knowledge, the effect of consolidation on the perceptual and motor characteristics of learning has received less empirical attention. The goal of the study in Chapter 3.4 (Hallgato et al., 2013) was to fill this gap by investigating how the offline period modifies motor and perceptual components of implicit sequence learning. This issue is of particular interest because it deals with the question of whether sequence learning and consolidation are mediated primarily by perceptual or by motor brain networks (N. Deroost & E. Soetens, 2006; Goschke, 1998). Hallgato et al.'s study investigated the role of 12-hour and 24-hour delay on the perceptual and motor components of implicit sequence learning using the ASRT-Race task while eliminating oculomotor learning. In addition, they aimed to explore the role of sleep in offline consolidation of these two factors of learning. Therefore, a 12-hour delay was administered between the learning phase and the transfer phase of the experiment, during which participants either slept (night group) or stayed awake (day group). They found significant sequence learning in the learning phase. Moreover, after the 12-hour and the 24-hour offline period, they found a significant learning effect in both the perceptual and the motor conditions; however, the transfer in the motor condition was more effective compared to the perceptual condition. They did not find any sleep effect on sequence learning in either condition.

The weaker consolidation of the perceptual component of sequence learning is in agreement with the results of Deroost and Soetens (2006) and Willingham (1999), who found evidence of perceptual learning only under specific conditions. According to several studies, perceptual learning only takes place when the structure of the sequence is simple, but in the case of deterministic sequences with second-order dependencies and probabilistic sequences with first-order dependencies, perceptual learning is absent or only weakly present (N. Deroost & E. Soetens, 2006; Mayr, 1996; Remillard, 2003). In addition, previous studies found perceptual learning in explicit conditions (Russeler & Rosler, 2000) and when a motor sequence was learned concurrently (Mayr, 1996). In Chapter 3.4's study (Hallgato et al., 2013), participants had no conscious awareness at all of the structure of the sequence. The only condition that met Deroost's (2006) criteria is that in the learning phase, participants learned the perceptual and motor components concurrently. Compared to Nemeth et al. (2009), who found similar magnitudes of perceptual and motor learning immediately after the learning phase, in Chapter 3.4 (Hallgato et al., 2013) we found a weaker perceptual learning effect in the transfer phase both after a 12-hour and a 24-hour delay. As the only difference was the 12-hour or the 24-hour delay, Hallgato et al. supposed that the differences between the results of the two studies can be related to the consolidation period only. Thus, this criterion, where in the Learning Phase, participants learned the perceptual and motor components concurrently, can be enough to infer that significant perceptual learning occurs immediately after the learning phase (B. Meier & Cock, 2010; Nemeth et al., 2009; Weiermann et al., 2010). However, it might also result in weaker consolidation after the delay period. One potential explanation for this is that brain structures underlying the perceptual and motor components of sequence learning are disconnected in the offline periods, and the perceptual component might be more sensitive to interference effects. To put the puzzle together, we propose that the consolidation period has a differential effect on the motor and perceptual components of sequence learning, so that in the transfer phase, the motor component is larger than the perceptual one. However, more investigations are needed to determine the potential background mechanisms of this phenomenon.

Beyond the question of the perceptual and motor components of learning, Hallgató et al.'s study (Chapter 3.4) has relevance for the sleep debate in consolidation as well (Debas et al., 2010; Doyon, Korman, et al., 2009; Gerván & Kovács, 2007; Karni, 1994; Robertson, 2009; Song, 2009; Stickgold & Walker, 2005; Walker et al., 2002). In this study we also found that sleep does not benefit sequence learning. In addition, the role of sleep in the consolidation of motor and perceptual factors of implicit sequence learning exhibits no difference. Another plausible explanation is that in the probabilistic sequence learning task used in this study, in addition to the primary sensory and motor brain regions, the subcortical structures and cerebellum are more involved (Doyon, 2008; Okihide Hikosaka et al., 1999; O. Hikosaka et al., 2002). This contrasts with the more basic finger tapping tasks, where sleep-dependent improvement has usually been found (Walker et al., 2002) (see also Chapter 3.1 and 3.3)

The effect of aging on consolidation

As implicit sequence learning is highly dependent on the integrity of the striatal network, and age-related structural and biochemical losses are pronounced in the striatal complex and connected prefrontal areas (Dennis & Cabeza, 2011; Raz et al., 2005; Anna Rieckmann & Bäckman, 2009), how online and offline sequence learning is affected by aging is an important question.

Several studies have shown that older adults exhibit online implicit sequence-specific learning comparable to young adults for simple repeating patterns in the SRT task (Brown, Robertson, & Press, 2009; Fraser, Li, & Penhune, 2009; Frensch & Miner, 1994; D. V. Howard & Howard, 1989, 1992). However, more recent studies have reported that although older adults can learn higher-order sequence structure, they show age-related deficits in doing so (Curran, 1997; D. V. Howard et al., 2004; J. H. Howard, Jr. & Howard, 1997; Nemeth & Janacsek, 2011; Nemeth, Janacsek, Londe, et al., 2010). For example, using a version of the ASRT task, Bennett et al. (2007) found that old persons were able to learn even third-order dependencies (1RR2RR3 where R is a random element), although they learned less than the young control group.

Only a few studies have investigated the consolidation of implicit knowledge in older persons (Brown et al., 2009; Fraser et al., 2009; Nemeth & Janacsek, 2011; Nemeth, Janacsek, Londe, et al., 2010; Siengsukon & Boyd, 2009a, 2009b; Spencer et al., 2007) (see Chapter 3.1 and 3.2). Spencer et al. (2007), for example, used an implicit contextual version of the SRT task in order to specifically examine the effect of sleep. In a previous study, they found sleep-related offline improvement in this version of the task among young adults (probably because it's contextual component; Spencer et al., 2006). In older subjects, however, neither offline improvement nor a sleep effect was shown (Spencer et al., 2007). Compared to young adults, elderly participants showed deficits in consolidation. Similarly, Brown et al. (2009) found age-related consolidation deficits using the classical version of the SRT task. Nevertheless, neither Spencer et al. (2007) nor Brown et al. (2009) could distinguish general skill learning from sequence-specific learning in their tasks. As the ASRT task has been shown to yield offline general skill learning, but not offline sequence-specific learning in young adults (Song et al., 2007b), it is important to differentially analyze these two aspects of implicit sequence learning in older adults as well.

In Chapter 3.1 we investigated implicit sequence learning after a 12-hour offline period (Nemeth et al., 2010). The novelty of this research in comparison to previous studies of consolidation in older adults (Brown et al., 2009; Siengsukon & Boyd, 2009a; Spencer et al., 2007) was that 1) it used probabilistic second-order sequences, and 2) it dealt separately with general skill and sequence-specific learning. The researchers showed that general skill learning improved offline in both the young and older groups, with the young group improving more than the old group. However, the improvement was not sleep-dependent, in that it was not relevant whether the 12-hour offline period included sleep or not. In the case of sequence-specific learning, they found no offline improvement in either group.

In Chapter 3.2, we investigated the consolidation of implicit sequence learning by comparing the performance after 12-, 24-hour, and 1-week delays from the initial learning session in young and elderly adults (Nemeth & Janacsek, 2011). In the young adults, the researchers found offline improvement of the general skill after all delays, with a gradual decline among them. The elderly adults showed offline improvement of the general skill only after the 12-hour offline period, and this improvement was weaker than that in the young group. Although the pattern in age groups is similar, these results suggest that the offline course of general skill learning may be affected by aging, since we did not find improvement either after a 24-hour or 1-week delay in the elderly group. No offline improvement was found in sequence-specific learning in either age group with any of the consolidation intervals. Sequence-specific learning did not decrease significantly between sessions for young participants, suggesting that sequence-specific knowledge was well consolidated in this group, whereas the older group showed weaker consolidation in all delay conditions compared to the younger group. Thus, according to these results, offline general skill learning is influenced both by the time course and aging, while the offline sequence learning is affected only by aging.

The differences between the young and old groups suggest that older participants are more sensitive to the time course in general skill learning, in that they showed no offline improvement even after the 24-hour delay. Regarding the practical consequences, the differences among the 12-, 24-hour, and 1-week consolidation intervals suggest that during new skill acquisition, it could be important to hold the training sessions closer together for optimal performance, with shorter intervals for elderly participants (Nemeth & Janacsek, 2011).

In the case of sequence-specific learning, older people show deficits both in online learning when the sequence structure is more complex and in the consolidation of sequence knowledge. A recent neuroimaging study (Dennis & Cabeza, 2011) found that elderly participants recruited medial temporal lobe structures in implicit sequence learning tasks, suggesting that compensation mechanisms are present to perform to an optimal level in these tasks. However, further studies are needed to precisely determine these compensation mechanisms and their potential role in age-related dementia and rehabilitation programs.

Conclusion and remaining questions

Taken together, we can conclude that consolidation is not a single process; instead, there are multiple mechanisms in the offline period (e.g. general skill, sequence-specific processes), which are differently influenced by the task demand, awareness of the sequence, the length of the delay period, perceptual and motor factors, and the age of the participant. Contradictions in this field can occur due to low or absent control of these factors of sequence learning. For example, sleep does not benefit sequence learning performance in the case of probabilistic sequences (Nemeth, Janacsek, Londe, et al., 2010; Song et al., 2007b), because such sequences are more complex and implicit compared to simple and explicit sequence structures such as those used in finger tapping tasks. Consequently, the awareness of the sequence structure can modify the role of sleep in the consolidation process (Robertson, 2009; Robertson, Pascual-Leone, & Press, 2004; Song, 2009).

The length of the delay period between the learning and testing phase is also an important factor that differentially modifies general skill and sequence-specific learning. In the case of general skill learning, the length of the delay is critical: The highest offline improvement is observed after shorter delay periods (Nemeth & Janacsek, 2011). In contrast, the delay period has less effect on sequence-specific learning: Retention of the previously acquired knowledge has been observed after one week (Nemeth & Janacsek, 2011) and even one year (Romano et al., 2010), but without additional offline improvement. Separating the perceptual and motor factors of learning can further elucidate this issue in that consolidation of motor sequence learning is more robust than perceptual factor of sequence learning. Nevertheless, more investigations are needed to replicate this finding and further detail its potential background mechanisms. Finally, one of the most important factors that must be taken into consideration is the age of participants, since several studies found significant age-related deficits in the consolidation of both sequence-specific and general skill learning in elderly adults (Brown et al., 2009; Nemeth & Janacsek, 2011).

Further studies of sequence consolidation should take these factors into consideration and investigate the following issues: 1) How consolidation affects implicit sequence learning in childhood in the separate cases of general skill learning and sequence-specific learning; 2) whether there is differential consolidation of the perceptual and motor factors of sequence learning in older ages; 3) how the length of delay modifies the consolidation of explicit sequence knowledge in the case of general skill and sequence-specific learning; and finally 4) whether the length of delay has a differential effect on perceptual and motor consolidation in the case of explicit sequence learning.

Ultimately, we know a lot about the biological background of online implicit sequence learning (Albouy et al., 2008; Dennis & Cabeza, 2011; Doyon, Bellec, et al., 2009; Keele et al., 2003; Kincses et al., 2008; Poldrack et al., 2005; Rieckmann et al., 2010; Sefcsik et al., 2009). However, there is a huge gap in our knowledge related to brain plasticity during consolidation. Future neuroscientific investigations should address this question, while controlling for the above-mentioned factors, especially the differentiation between general skill and sequence-specific learning. These distinctions can contribute to developing a more sophisticated picture of brain-consolidation-behavior interactions.

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