Eötvös Loránd University

Faculty of Education and Psychology

Personality and Health Psychology Doctorate Programme

Director of programme: Oláh Attila, Professor

Competitive and cooperative mechanisms in implicit and explicit learning and memory processes

Candidate: Márta Virág

Supervisors: Karolina Janacsek PhD, Dr. Dániel Fabó PhD

Consultant: Dezső Németh habil. Associate Professor

Dissertation commitee

Defence chair: Márk Molnár Dsc HAS

Secretary: Gyöngyi Kökönyei PhD

Internal opponent: Anikó Kónya habil. Associate Professor

External opponent: Demeter Gyula PhD

Commitee members: Ildikó Király, habil. Associate Professor; Gyurgyinka Gergev PhD; István Winkler Dsc HAS; Péter Simor PhD

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Introduction and aims

The ultimate reason of the evolution of the centralized nervous system is to provide the organism the ability to perform adapted behavior to environmental needs. This adaptation is what we call learning and memory. Neural systems are designed to adapt to the constant change of the surrounding environment, even very primitive organisms with simple neural systems can perform such neural plasticity via changing the synaptic weights between interconnected neurons (Brown et al., 2013). The mechanism of short-term and long-term learning and memory are very similar in highly developed animals and humans including modulatory neurotransmitters like serotonin (McEntee and Crook et al., 1991, Mazer et al., 1997), intracellular changes of special proteins like amyloid (Nitta et al., 1994, Lesné et al., 2006), and glial mechanisms (Hyden and Egyházi et al, 1963, Sampaio-Baptista et al., 2013, Zatorre et al., 2012). Plasticity is the basic feature of the central nervous system, furthermore there are special networks in the brain, developed to create optimal conditions for the emergence of more complex associations in learning and memory. A good example for this is the learning capacities of vertebrates, enough to consider the adaptation potentials of craws (Bugnyar and Kotrschal et al., 2002) and rats (Jarrard et al., 1993). Still, the vast majority of the neuroscience focuses on the mechanism of learning and memory, gaining substantial understanding of the underlying cellular and network mechanisms.

Neurodegenerative diseases in which memory performance drops the earliest are considered the most impacted healthcare issues in the increasingly aging population worldwide (James et al., 2010). The broken synaptic and cellular machineries in these conditions are well known (Pozeuta et al., 2013) along with the affected anatomical structures in the brain (Tondelli et al., 2012). Memory loss is an obvious change in neurodegenerative disorders such as Alzheimer's Disesase (Jahn et al., 2013), due to the impairment of the MTL. Still, there is a lack in the literature of the impaired network mechanisms that stand behind these functional losses. To address this question, we selected different pathological states where selective loss of cognitive functions, such as memory, or changes in overall cognitive functioning are the key features of the neuropsychological impairment and studied both behavioral and electrophysiological changes.

The aim of this doctoral work is to give a better insight of how implicit and explicit learning and memory processes are related to one another. Our objective was to gain better understanding of the specific brain areas involved in these processes. Also, we were interested in how these processes can possibly overlap, and the rather complex pattern of cognitive decline that can possibly come with the impairment of such overlapping areas. Until now, we

approached these questions by testing implicit/automatic vs. explicit/controlled cognitive processes, including learning and memory capabilities of multiple patient groups with different psychiatric or neurological conditions.

Neuropsychology has been greatly supported by the evolution and expansion of modern brain imaging techniques. As a result, our knowledge about cognitive functions and their relation to specific brain areas has been growing over the past decades. Certain syndromes and diseases of the nervous system have shown us that specific neural impairments result in specific cognitive deficits or even alter one's personality. From patient H.M. to date, we have learned that memory formation and storage relies on multiple cognitive functions and multiple areas within the brain.

In the following introductory sections, I will describe classical and more recent theories on learning and memory, separately mentioning implicit and explicit learning and memory, followed by interactive learning and memory processes, and the neuropsychology of implicit and explicit learning. In the end of this section, I will posit my research questions based upon the reviewed literature.

Background

1. Learning and memory

Classical learning and memory theories primarily distinguish memory systems according to storage capacity: sensory memory, short-term and long-term memory. Long-term memory is traditionally further divided into declarative and non-declarative memory according the brain areas they rely on, and the content of the memories they encode. Declarative memory has been associated mainly with the medial temporal lobe (MTL), while non-declarative memory relies mostly on the fronto-striato-cerebellar network (Tulving et al., 1994, Reber and Squire et al., 1994), however these strict topographical distinctions are somewhat outdated (Henke et al., 2010). This will be further explained in later sections dealing with overlapping learning and memory networks.

According to these traditional models, declarative/explicit memory is further separated into episodic and semantic engrams, depending on the content of the information (personal, autobiographical memories in episodic versus general knowledge in semantic memory). Non-declarative/implicit memory can also be divided into subcategories, also depending on the content of the information and on the type of memory task used: procedural memory, priming, classical conditioning and non-associative learning, etc. (see Figure 1). Classical theories distinguish implicit and explicit memories according to intention (controlled versus automatic actions), awareness (conscious versus unconscious actions), the directedness of a possible task setting (direct test versus indirect test setting, reflecting a difference in knowledge of the participant and the experimenter), and behavior (accuracy versus priming) (Schacter et al., 2000; Squire et al., 2004).

Explicit vs. implicit learning and memory have been often used as overlapping terms with declarative and non-declarative memory, respectively - this distinction primarily depends on the presence or lack of awareness during learning and use of the acquired knowledge (Squire and Zola et al., 1996). Note that although these concepts do not overlap entirely, similarly to previous literature, here we will use them interchangeably. The implicit and explicit distinction in our line of work contains further important information, as it also refers to the lack or presence of awareness during learning and recollection.

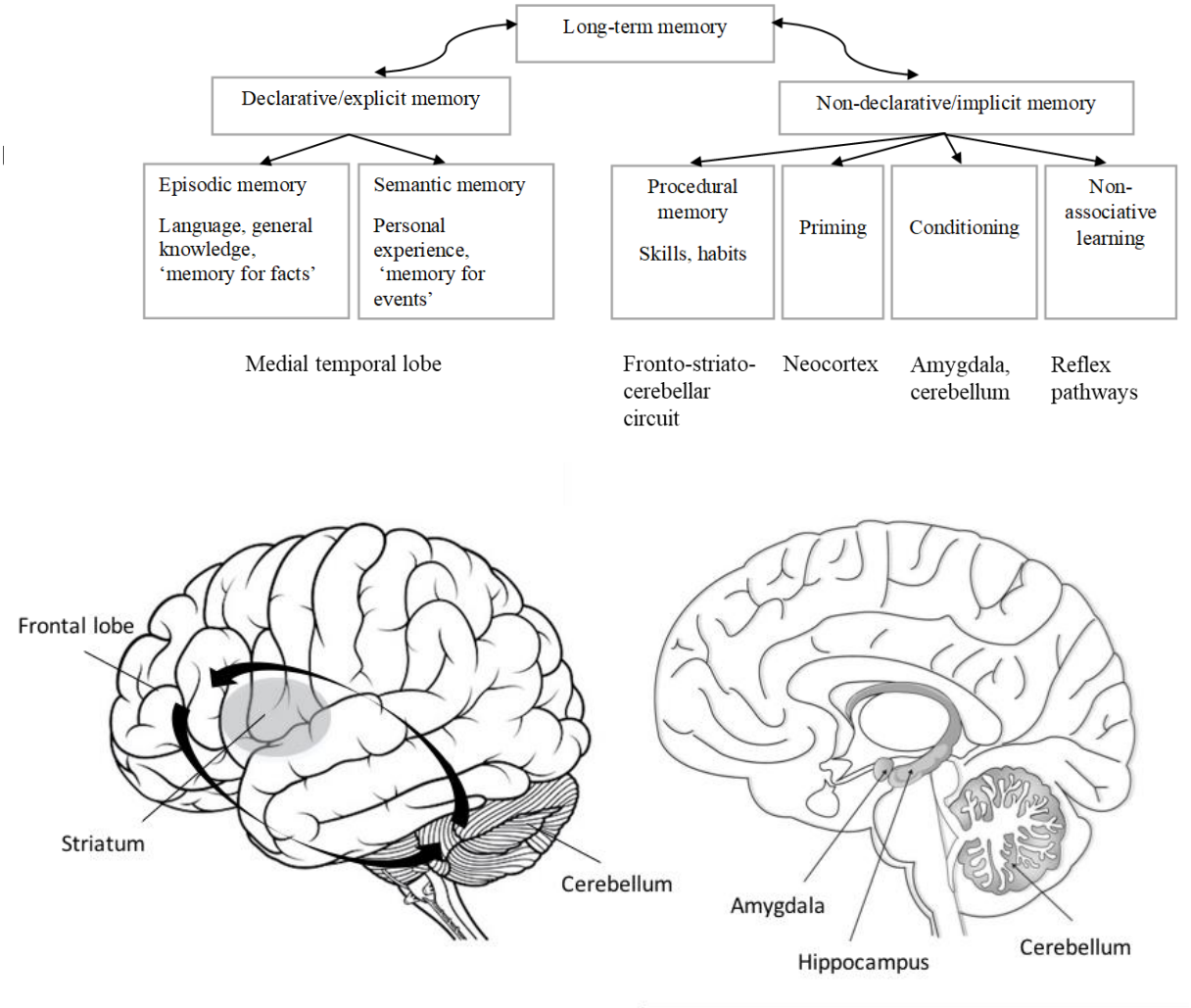

Figure 1. Subdivisions of long-term memory and their localization within the brain according to classical theories.

Importantly, different memory tasks target different but possibly overlapping learning and memory processes, therefore no experimental results should be generalized exclusively to one memory process – as referred to in the classical theories of learning and memory. Explicit awareness can appear in implicit memory processes, also awareness is not always present in explicit learning processes, for example in word-list learning, participants tend to use implicitly embedded tactics to improve performance (Winne et al., 1996), thus the need for deliberate self-regulation decreases with knowledge. Or, explicit (directed) instructions to a task can promote implicit learning processes in second language learning tasks (Ellis et al., 2002). However, there is also evidence for the contrary, in that there is no need for explicit knowledge in an implicit probability sequence learning task (Reber et al., 1989, Song et al., 2007a). Also, some authors state the acquisition of implicit and explicit knowledge happens parallel, thus explicit knowledge of an implicit task sometimes has no impact on implicit performance at all

(Willingham and Goedert-Eschmann et al., 1999). Such an overlap between implicit and explicit processes in learning and memory further strengthens the notion that completely encapsulated cognitive processes are very hard to find, especially outside of an experimental setting.

In a similar line of thought, it has been suggested that different learning and memory processes have overlapping features, and the traditional distinctions are too strict to replicate learning and memory processes in real life (Henke et al., 2010). Henke and colleagues proposed a framework in which the rigidness of the associations and the speed of encoding determine which networks of the brain get involved in a specific learning process, instead of only consciousness as a primary discriminatory factor, which they believe to be a non-sufficient criterion if there are no other factors. They differentiate between rapid encoding of flexible associations, slow encoding of rigid associations and rapid encoding of single items. In this sense, non-declarative/implicit learning falls into the second category, in which slow encoding of rigid associations happen, relying mainly on the basal ganglia, the cerebellum and the neocortex. However, there is also evidence suggesting that within non-declarative/implicit learning, the MTL also has a role, especially in the initial phases of learning. Experiments with amnesic patients have shown that there is deficit in implicit learning of contextual information, which suggests a role of the hippocampus in implicit learning processes (Chun and Phelps et al., 1999). Also, functional magnetic resonance imaging (fMRI) studies found an increase in activation in the MTL areas during an implicit learning task (Schendan et al., 2003; Moody et al., 2004, Wang et al., 2010). Furthermore, behavioral experimental data shows that in Mild Cognitive Impairment (MCI), there is an impairment in implicit learning, especially in the initial phases, also suggesting MTL involvement. In summary, the hippocampus can also play a role in procedural learning processes, pointing out that it is not only involved in the formation of more flexible associations, but it is also involved in the initial encoding phases of more rigid associations.

2. Implicit/non-declarative learning and memory

2.1. Characteristics of implicit/non-declarative learning and memory

Implicit learning is a complex, incidental mode of information coding, in which awareness of the content and its influence on behavior is partially invisible (Nissen and Bullemer et al., 1987). Our line of work included procedural learning paradigms, mostly

focusing on skill learning (Figure 1). Procedural memory is an essential mechanism for the acquisition of motor, cognitive and social skills. Such skills govern our ability to adapt our behavior effectively to our environment. Most of the times, the development of these skills remains implicit, which is why we only realize the presence of a certain skill or automatism when it is already embedded into our behavior. The lack of awareness in both learning and recall can also result in rigid associations, which can be difficult to modify, and at the same time are very resistant to forgetting (Berry et al., 1991, Henke et al., 2010). The way in which these skills develop and interact with other cognitive processes/functions is crucial to understand how skill learning occurs, and how our capacities change over the course of years or as maturation of the brain proceeds. It is important to think about cognitive tasks and the performance of participants as a fine-tuned result of multimodal processes involving multiple cognitive functions. From an experimental point of view, implicit learning can be specified as 'accidental' (incidental) acquisition of dependencies or co-occurrences of stimuli that is expressed through performance only (Rieckmann et al., 2009).

Reber and colleagues (2013) described implicit learning as a form of a more general plasticity process, which is connecting processing networks that adaptively improve function via experience, instead of an encapsulated cognitive process. According to their theory, implicit learning in general is an improvement in experience-based knowledge in a wide network of the brain, including cortical areas, as well as the MTL, indicating cortical plasticity of those brain areas, which also depends greatly on the task or the situation itself. This model is innovative in the sense that it doesn't narrow down implicit learning as a closed process within the brain, furthermore, it shows that implicit learning is a process of alterations instead of "just" stimulus-response learning. Cleeremans and colleagues (1997, 1998) distinguished sub-functions of three levels of implicit learning, further showing it as a process that goes through changes over time. In their opinion implicit learning situations typically involve three components: (1) exposure to some complex rule-governed environment under incidental learning conditions; (2) a measure that tracks how well subjects can express their newly acquired knowledge about this environment through performance on the same or on a different task; and (3) a measure of the extent to which subjects are conscious of the knowledge they have acquired. Three paradigms that follow this conceptual design have been extensively explored: artificial grammar learning, sequence learning, and dynamic system control. We will mainly focus on sequence learning as the empirical studies of the thesis tested sequence learning as well.

Implicit sequence learning is one of the most well researched topics in this field, reflecting implicit learning processes by showing how our brain picks up regularities of the occurring stimuli (Howard and Howard et al., 1997). Serial reaction time tasks (SRT) have been excessively used as a measure of implicit sequence learning, as it is based on such accidental knowledge, without explicit awareness (Shanks and St. John et al., 1994). Sequences are a connected series of events (Robertson et al., 2007), thus they reflect how our behaviour is temporally organized. Also, by perceiving that events are sorted according to a rule, higher order associations are also formed, thus future elements can be predicted (Keele et al., 2003). In a typical SRT task, participants are instructed to respond as fast and accurately as possible to the stimuli that has been presented to them, while the structure and the sequence are unknown by the participants. Note however, that there is evidence that explicit knowledge of the sequence induces faster RTs (Frensch and Miner et al., 1994), however there is also evidence that implicit and explicit knowledge of a sequence are independent of each other (Reber and Squire et al., 1998), suggesting that there is no direct relation between implicit and explicit knowledge of something. In later sections, I will specify the networks and phases of learning through which implicit and explicit processes can be related.

In the SRT tasks, general skill learning is typically measured by the reaction time (RT) decrease over practice, while sequence specific knowledge is computed by the difference between reaction time (RT) to the elements of the sequence versus random stimuli (Nissen and Bullemer et al., 1987). Participants can learn sequences in the SRT tasks either incidentally/implicitly or with explicit instructions; thus, participants can be unaware or aware of the underlying sequence, respectively (Janacsek and Nemeth et al., 2012; Howard and Howard et al., 1997).

Consolidation of implicit knowledge mostly depends on the time elapsed after learning occurred, however there has been a debate about the possible role of time spent in sleep in the consolidation of implicit memories as well (Robertson et al., 2004; Mednick et al., 2009; Albouy et al., 2013). Implicit sequence learning seems to be rather *sleep-independent* in a healthy population (Robertson et al., 2004; Nemeth et al., 2010a), as the acquired knowledge seems to be similarly well consolidated after on "offline" period that included nighttime sleep or daytime wakefulness. Recently, others also failed to find sleep related differences in consolidation of healthy children and children with sleep disorder (Csabi et al., 2016).

2.2. Neural background of implicit/non-declarative learning

Implicit sequence learning relies mostly on fronto-striato-cerebellar networks of the brain (Doyon et al., 2003; 2009; Henke et al., 2010; Klivenyi et al., 2012; Thach al., 1992; Fiez et al., 1992), however the exact involvement and roles of these areas in learning are still debated. Depending on the nature of the task itself, multiple cognitive functions can be involved at the same time, resulting in the activation of multiple areas in the brain. Such functions include attention-dependent executive functions and perceptual processes as well, depending on the modality of the task. Although implicit sequence learning and memory has been mostly associated with fronto-striato-cerebellar networks (Schacter et al., 1997), increasing evidence suggests the importance of the medial temporal lobe (MTL) (Chun and Phelps et al., 1999) as well. In the following sections, I will line up experimental evidence on the role of the frontal lobe, the striatum and the MTL in implicit learning processes. There are multiple reasons behind choosing frontal, striatal and temporal involvement as a focus of this work. First, striatal involvement is the 'cornerstone' of implicit learning processes (Doyon et al., 2003, 2009). Frontal involvement modulates how these functions progress (Grafton et al., 1998; Peigneux et al., 2000), thus we were interested to view literature on how a specific amount of frontal lobe involvement gives the best implicit learning results. Possible MTL involvement was also added to our focus, as previous results have suggested that besides the fronto-striato-cerebellar network, MTL regions might also contribute to this type of learning, and we were eager to see what the MTL adds to implicit learning processes. The cerebellum will not be in the focus of this work, as its role in implicit learning processes through motor control (Fiez et al., 1992) is clearer.

2.2.1. Frontal lobe involvement in implicit/non-declarative learning

Frontal lobe involvement in implicit learning processes has received increasing attention in cognitive research over the past two decades. An increase in cerebral blood flow, thus heightened activation had been found with Positron Emission Tomography (PET) in frontal lobe areas when attending an SRT task (Rauch et al., 1995; Grafton et al., 1996; Peigneux et al., 2000). Importantly, explicit attempts to learn a more complex alternating sequence produces a decline in core implicit learning performance, moreover, explicit search itself results in an even greater frontal lobe activation measured by fMRI. These results suggest that explicit search in an SRT task results in heightened frontal lobe activation, which seems to have a deleterious effect on implicit learning processes (Fletcher et al., 2005).

A great number of researchers have tried to shed light on the exact relationship between frontal lobe networks involved in implicit sequence learning and executive functions, by taking a closer look at patient populations with frontal lobe impairment. For example, Beldarrain and colleagues (2002) investigated the relationship between prefrontal cortex related (PFC) cognitive functions and visuomotor sequence learning (measured by the SRT task) as well as perceptual learning task (measured by the Pursuit Tracking Task containing a pattern tracking subtask measuring explicit motor sequence learning and a random tracking task measuring perceptual learning - PTT) in patients with PFC lesions and healthy controls and found that patients with PFC lesions performed worse on the SRT task as well as on the pattern tracking task of the PTT, suggesting an important role of the PFC in sequence learning processes. Overall, the authors concluded that the PFC is involved in both more explicit and more implicit sequence learning setups, also, PTT correlated with planning functions, while performance on the SRT task correlated with working memory performance, suggesting that different PFC regions may be selectively involved in visuomotor sequence learning, depending on the cognitive demands of the specific tasks. The importance of the intactness of the PFC in implicit learning processes was further stressed in an experimental setup looking at the role of the corpus callosum (de Guise et al., 1999). The experiment was based on an SRT task, which involved either bimanual or unimanual key-pressing responses to measure bilateral and unilateral sequence learning of acallosal patients and healthy controls. According to the results, the unilateral sequence learning task not only requires the integrity of frontal, striatal, and cerebellar areas, but (especially) the anterior part of the corpus callosum as well. The authors argue that this area has a very important regulatory effect within the frontal-striatal-cerebellar loop, regulating implicit sequence learning capabilities as well.

It is also possible to measure the relationship between implicit learning and PFC related cognitive functions such as working memory or executive functions by relying on experimental paradigms only. Feldman and colleagues (1995) did not find a correlation between performance on an SRT task and working memory performance measured by span tasks (forward and backward Digit Span Tasks) and the Wisconsin Card Sorting Task (WCST). Importantly, many others tried to explore the relationship between working memory performance and implicit learning performance, and failed to find a relationship (Kaufman et al., 2010; Frensch and Miner et al., 1994). Janacsek and Nemeth (2013, 2015) reviewed literature in this topic and concluded that the relationship between sequence learning and working memory depends greatly on the explicitness of the sequence in the SRT tasks, the method with which working memory capacity is measured, whether online or offline stages of sequence learning are tested,

and which aspects of sequence learning, such as general skill learning or sequence specific knowledge are measured.

It appears that executive functions can interfere with implicit learning processes, proven by a dual task paradigm (Foerde et al., 2006), by adding a distracting secondary task following sequence learning (Brown and Robertson et al., 2007), by using hypnosis to reduce the engagement of frontal lobe functions (Nemeth et al., 2013b), or when conflicting goals are present within one task (Blackwell et al., 2014). In the following introductory sections, these experiments will be presented as an example of competitive cognitive functions.

In summary, it appears that the frontal lobe, especially the PFC is involved in implicit learning processes, even if the underlying sequence is completely hidden for the participants, thus the task is completely implicit (Rauch et al., 1995). Also, studies found that greater involvement of the PFC results in better performance on an SRT task, suggesting that the intactness of the PFC may play an important role in implicit learning paradigms (Grafton et al., 1998; Peigneux et al., 2000). However, there is also evidence for a lack of direct relationship between working memory and implicit learning performance (Kaufman et al., 2010; Janacsek and Nemeth et al., 2013). Moreover, there is evidence for an interference (Nemeth et al., 2013; Blackwell et al., 2014) between frontal lobe mediated executive functions and implicit learning processes, implying that there is a fine balance between frontal lobe mediated cognitive resources and cognitive resources for implicit learning. It is possible that this balance is regulated by general cognitive abilities (Pretz et al., 2010), relying greatly on the exact tasks measuring the relationship between these functions (Janacsek and Nemeth et al., 2013, 2015).

2.2.2. Striatal involvement in implicit learning and memory

Striatal involvement in implicit learning has been extensively investigated in the previous years (Oishi et al., 2005; Rauch et al., 1997; Willingham et al.,1998; Peigneux et al., 2000; Doyon et al., 2009). Functionally, the striatum can be divided into an associative and a sensorimotor circuit. The associative circuit (situated in the more anterior area of the striatum) has been hypothesized to be more important for the initial phases in a motor sequence learning task, when executive control demands are greatest, followed by a shift to the sensorimotor circuits of the striatum (when motor control takes over) (Doyon et al., 2009). Also, when comparing random and implicitly hidden sequences in an SRT task setting in fMRI, Reiss and colleagues (2005) found increased striatal involvement during the implicit sequence learning trials, which affected both dorsal and ventral striatal areas, however ventral striatal activation elicited stronger activation in implicit trials compared to baseline (random) trials, which is in

line with the previously mentioned results showing greater activation in the ventral striatal areas results in better performance on a motor sequence learning task. In line with these results, Penhune and Steele (2012) suggested that the striatum is important for developing (probabilistic) associations between individual items and that these associations evolve with practice.

Striatal involvement in implicit learning can be further specified by looking at specific patient populations with striatal dysfunction, for example in patients suffering from Parkinson's Disease (PD), brain scans typically show pronounced cell death in the basal ganglia (Davie et al., 2008). PD patients were compared with patients with pronounced cerebellar or frontal lobe lesion in an SRT task, in which the fixed 10-element sequence was embedded within the task and explicitly told to the participants, thus, they had explicit knowledge of the 10-element sequence (Doyon et al., 1997). Importantly, PD patients and patients with pronounced cerebellar lesion failed to improve their performance late in the acquisition process, suggesting that incremental acquisition of a new visuomotor skill depends upon the integrity of both the striatum and the cerebellum, but not of the frontal lobes. Similarly, Smith and McDowall (2006) concluded that PD patients show sequence learning on an SRT task, however their decrease in performance is due to the failure to integrate the sequence, which is a consequence of basal ganglia damage. Doyon and colleagues (2003) conducted a systematic review mostly relying on the previously mentioned investigation with patient populations. Overall, they found that such implicit or experience-dependent processes differ in the qualities of the new information – whether it is new sequence of movements (such as motor sequence learning) or a new environmental perturbation (such as motor adaptation). Doyon and colleagues (2003) have proposed that during the initial phases of learning, the cortico-striatal and cortico-cerebellar systems have a separate role in motor sequence learning and motor adaptation. Importantly, such differences remain in the automatization and retention phases of learning processes, indicating that the motor cortical regions and the parietal cortex are important in both cognitive processes, while striatal and cerebellar activity dissociate between motor sequence learning and motor adaptation in the automatization and later recall phases.

There is also evidence for a compensatory mechanism of the MTL regions in case the integrity of the striatum is declined. Such experimental paradigms show most pronounced results when brain network activation patterns and learning performance of healthy controls are compared to patient groups with striatal disfunction (Moody et al., 2004, Rauch et al., 1997). Rauch and colleagues investigated the role of striatal function in a series of experiments by using an SRT task and measuring simultaneous PET activation in obsessive compulsive

disorder (OCD) patients (Rauch et al., 1997). In their study, Rauch and colleagues found a bilateral ventral striatal activation in healthy control participants during performing an SRT task, which was absent for the OCD group. These results are in line with previous results using fMRI (Lehéricy et al., 2004), showing an increase in ventral striatal areas after certain amount of practice in the SRT task. On the other hand, patients with diagnosed OCD with hypothesized cortico-striatal dysfunction were lacking such striatal activation, and showed bilateral temporal activation, which Rauch and colleagues interpreted as a compensatory mechanism instead. On a similar note, Rieckmann and colleagues (2009) conducted a review on implicit learning in healthy aging and found that implicit learning is normally spared in older ages. The authors suggested that intactness of implicit learning in older ages probably reflects a reorganization process, during which - as a compensatory mechanism - cortical and MTL structures take over declined striatal functions. A shift of increase in activation towards MTL regions instead of the striatum and a slight decline in performance has been observed with other implicit learning tasks as well, for example in covariation learning, and during the weather prediction task for PD patients compared to healthy controls (Moody et al., 2004).

To sum up, striatal involvement in implicit learning processes has been shown via imaging studies (Lehericy et al., 2004; Reiss et al., 2005; Doyon et al., 2009), as well as experiments relying on patient populations with striatal dysfunction, by showing a decline in implicit learning performance (Doyon et al., 1997; Moody et al., 2004), as well as altering brain activation patterns (Rieckmann et al., 2009; Moody et al., 2004). Such shifts in activation patterns raise the notion that besides the classical fronto-striato-cerebellar network, the MTL region also has to be taken into account when considering the brain networks implicit learning processes rely on.

2.2.3. Temporal lobe involvement in implicit learning and memory

As it was mentioned above, the role of the medial temporal lobe (MTL) has been mostly suggested in explicit learning processes, however, implicit learning processes are also in the focus of research (Chun and Phelps et al., 1999; Schendan et al., 2003). Involvement of the MTL in implicit learning processes can be investigated by studies using fMRI to localize areas involved during cognitive engagement or by taking a closer look at implicit learning performance of patient populations with MTL damage. Also, further information on the role of the MTL in implicit learning can be extracted by looking at multiple neuropsychological tests aiming to dissect certain subprocesses of implicit learning.

Reber and colleagues (1998) compared amnesic patients and healthy individuals on a 12 element SRT task (measured by a decrease in RT) and explicit test performance (measured by recognition of the sequence) and found that amnesic patients exhibited better performance on the implicit task and impaired performance on the explicit task. The authors concluded that implicit and explicit knowledge of the embedded sequence are separate and depend on different brain systems, indicating that explicit sequential knowledge depends on MTL regions, and thus is impaired for the amnesic patients, while implicit learning performance is independent of the MTL. These results suggest that explicit and implicit processes rely on distinct brain areas, as explicit task performance is impaired compared to the implicit performance. However, one cannot rule out the role of the MTL in implicit processes as well, as this study compared the two learning mechanisms in an MTL impaired population and is lacking a comparison to healthy controls in relation to both implicit and explicit processes. Some years later, Schendan and colleagues (2003) investigated the presence of common neural involvement in both explicit and implicit processes, using an SRT task with both implicit (without awareness) and explicit (participants knew the sequence) task settings, in healthy young adults. Importantly, participants showed an increase in the activation of the MTL in both explicit and implicit task settings, suggesting that the MTL region has a role in implicit learning processes. The contrast between the previously mentioned results requires some explanation. The fact that there was an activation in the MTL during an implicit task setting suggests that the MTL is involved in implicit learning processes, however performance seemed intact in an MTL impaired population. This is probably due to the fact that the MTL is involved in the initial phases of implicit learning, and later on activation shifts to the fronto-striato-cerebellar network (Schendan et al., 2003). On a similar note, Rose and colleagues (2002, 2011) suggested that implicit learning of sequence regularities happens with the help of MTL regions, while fixed stimulus-response associations (motor learning) relies mostly on the activation of the basal ganglia. Moreover, Robertson and colleagues (2007) implied that the engagement of the MTL is related to the computational requirements of that task. The role of the MTL has been suggested to be more prominent in the processing of contextual information within a sequence (Shanks et al., 2006, Rose et al., 2002, 2011).

The role of the MTL in implicit learning can further be specified in populations with MTL deficit. For example in an experimental setup comparing amnesic patients and healthy controls, Vandenberghe and colleagues (2006) found that healthy controls perform well in an SRT task containing a more deterministic (with two fixed 12 element sequences in fixed location within the task) and a more probabilistic task setting (with the same 12 element

sequences, but their appearance was not fix within the task, as it followed a statistical order). Performance of amnesic patients decreased greatly in the probabilistic condition and remained stable on the more deterministic condition. These results suggest that implicit learning is spared in amnesia, but only to a certain extent, as a decrease of performance in the more probabilistic condition suggests that amnesic patients have difficulty adapting their implicit knowledge in a task setting that requires a more flexible processing mode. Similarly, Shanks and colleagues (2006) investigated the role of MTL in implicit sequence learning in two studies, comparing healthy individuals with patients suffering from organic amnesia, and by inducing an artificial amnesic state pharmacologically induced (by diazepam) in healthy individuals. In both studies, participants conducted the SRT task. Overall, the results of the two studies revealed that sequence learning is spared in both organic origin and diazepam-induced (although it is dose dependent, with higher doses leading to more impairment) amnesia, but the expression of sequence knowledge is impaired, meaning that it takes more elements in a sequence to perceive it as a sequence and to induce priming. This indicates that MTL deficiency results in a decrease mostly in the learning of contextual information.

The contextual aspects of implicit learning and memory have been in the focus of neuropsychological research, especially it's relation with MTL structures. Amnesic patients with hippocampal damage using the contextual cueing task (Chun and Phelps et al., 1999) show deficits in recording the contextual information, but show intact implicit learning performance at the same time. The authors concluded that this is because the hippocampal formation encodes contextual information, regardless of the presence or lack of conscious awareness during learning (Chun et al., 2003). Later, Wang and colleagues (2010) also pointed out the importance of the MTL regions, specifically the perirhinal cortex in a series of conceptual priming experiments, including category generation and semantic decision making. Amnesic patients with impaired MTL regions showed decline in the conceptual priming experiment, which was further confirmed by the same group of researchers, recording an increase in activation during a conceptual priming task in healthy adults with an fMRI setting. These results suggest that the decline found in the performance of amnesic patients by the same group of researchers is in fact due to the MTL impairment.

Certain neurodegenerative diseases, such as dementia and Parkinson's disease (PD) have also been in the focus of research. As previously mentioned, PD patients showed heightened activation of the MTL when performing the weather prediction task in an fMRI task setting (Moody et al., 2004), indicating that due to the impairment of the basal ganglia in PD, MTL regions can compensate for the lost functions. These results further strengthen the notion

that explicit and implicit memory systems interact, especially, when the activation of certain brain areas decreases due to the course of an illness.

Both behavioral and neural evidence has been growing over the years on the overlapping characteristics of implicit and explicit memory processes, overruling the classical views on separate memory systems. In summary, experimental evidence on this topic suggests that the MTL is a region important in the initial phases of processing contextual and relational information of stimuli. This happens irrespective of the presence of awareness, implicating that it is an important area for both explicit and implicit learning processes.

3. Explicit memory and learning

3.1. Characteristics of explicit/declarative memory and learning

Explicit learning and memory refer to cognitive processes in which the formation of an engram may occur in a conscious way (Squire et al., 1992). In addition to consciousness in the encoding phase, explicit memories can be consciously recalled as well. According to previous models on learning and memory, explicit memory processes underlie declarative memory, and within that, both semantic and episodic memories. As mentioned earlier, semantic memories refer to a general knowledge of the outside world (McRae et al., 2013), such as knowledge of history or arts, registering cognitive referents of stimuli from the environment (Tulving et al., 1972). Episodic memories, on the other hand, refer to one's personal experience (Tulving et al., 2002), such as personal memories. Importantly, unlike semantic engrams, episodic memories have spatial (where the event took place) and temporal (the associative link between chain of events that defines time limits of a memory) components (Tulving et al., 1974). Such memories can be retrieved in form of recognition as well as by free or cued recall (Tulving & Wiseman, 1975; Eichenbaum et al., 2007). Recognition of a previously displayed item and free recall require distinct neural and cognitive effort as well as common areas, such as the PFC (Staresina and Davachi et al., 2006). Importantly, forgetting also differentiates between free recall and recognition processes, further depending on the rate of relatedness of items within the engram (Gómez-Ariza et al., 2005). Also, recognition and recollection differ in hippocampal involvement as well (Eichenbaum et al., 2004). Recognition failure can equally happen to semantic as well as episodic memories (Neely et al., 1983).

Explicit memory is often assessed by neuropsychological tests, which probe memories in the verbal or visual domain. "Memory in Reality", thus memory that is closer to everyday

situations, and “Behavioral Memory”, thus behavioral performance in memory tasks have been tested in patients with temporal lobe epilepsy and in healthy control participants (Helmstaedter et al., 1998) to see how “behavioral memory” reflects “memory in reality”. This study aimed to show that subjective self-reports of remembering something might not reflect correct memory performance. According to these results, memory in reality is more susceptible to forgetting, as there was a slight difference between the subjective feeling of remembering the learned material and the actual performance. The authors argue however, that recollection can be easily boosted by enhancing familiarity. Also, Helmstaedter and colleagues argue that behavioral memory and memory in reality yielded similar results behavioral memory testing is therefore a valid indicator of explicit memory performance.

Visual explicit memory can be tested by exposing one to abstract or concrete images, which can be later recalled or recognized from a set of images. Also, testing visual memory with a set of images, associated as a scene is also possible, further testing relational memory as well (Castelhano et al., 2005; Hollingworth et al., 2006). One of the most commonly used visual memory task is the Rey Complex Figure Test (Rey et al., 1941), which includes a copy, an immediate recall and a delayed recall session of an abstract image. Other commonly used tasks include the Benton Visual Retention Test (Benton et al., 1950), which mainly focuses on the spatial aspects of visual explicit memory.

One of the most common ways to test verbal explicit memory is by teaching participants lists of words, and later asking them to recall it. The auditory version of the Rey Auditory Verbal Learning Test (Rey et al., 1964) is widely used, validated task, measuring this effect. This test requires learning of a list of 15 unrelated concrete and highly frequent words (list A) in 5 consecutive learning trials, where each learning is followed by an immediate recall of all the words remembered. Subjects then are distracted by the learning and immediate recall of a second word list (list B) in one trial (distraction trial). This distraction is directly followed by the free recall of list A. Another free recall of list A is requested after a delay of 30 minutes. Following this delayed free recall, patients are asked to recognize the words of list A out of a list which consists of words from lists A and B in addition to words that are not related to the words of list A and B. The Rey Auditory Verbal Learning Test is a clear way of measuring explicit learning processes, thus it has been extensively used in the past with patients having different cognitive impairments, such as dementia (Ricci et al., 2012), ADHD (Pollak et al., 2007), Parkinson’s Disease (Postuma and Gagnon et al., 2010), etc., as well as amongst healthy

individuals (Sziklas et al., 2008; Jafari et al., 2010), leading to a widespread literature. We also used a modified version of this task in one of our experimental setups (see later in Study III.).

3.1. Neural background of explicit/declarative learning

According to lesion studies and reports on explicit learning capabilities of amnesic patients (Scoville and Milner et al., 1957), declarative memory depends on the integrity of brain structures and connections mostly in the MTL and the diencephalon (Squire et al., 1992), although it has been suggested that other areas of the brain are also important in this type of learning and the consolidation of such memories, such as the amygdala (Cahill and McGaugh et al., 1998) or neocortical structures that mediate short-term memory as well as the retrieval from long-term storage (Eichenbaum et al., 1991). These neocortical areas include projections from the MTL to frontal lobe areas, mainly the prefrontal cortex (PFC) (Preston and Eichenbaum et al., 2013).

Importantly, depending on the content of the information, retrieval and encoding can rely on slightly different areas (Eichenbaum et al., 2007). Perceptual information about objects and events, thus information on "what" the perceived item is are first processed according to their sensory modality (vision, hearing, touch or olfaction). This information then projects to association cortical areas (temporal, parietal, and other cortical areas), followed by a projection to the perirhinal and lateral entorhinal cortex. Here, multisensory information converges into one engram, as the MTL is responsible for the binding of information. Information about 'where' in space events occur, thus the contextual information is processed in a slightly different cortical stream. Associations happen at the posterior parietal, retrosplineal and other cortical areas, following a projection to the parahippocampal and medial entorhinal cortex . The "what" and the "where" streams then converge in the hippocampus. It is important to note here, that - as stated in previous sections - contextual information is also important in implicit learning processes. Encoding of the context of the information is related to the MTL, irrespective of the rate of explicitness in a task. Also, the MTL is responsible for the binding of information, thus, to construct relational memory, also irrespective of explicitness of a task. This may also explain the role of the MTL early in initial phase of implicit sequence learning.

The hippocampus also supports declarative learning and memory in sparse ways. For example, it boosts associative processes between separate memory engrams (Squire and Zola-Morgan et al., 1991), as well as pattern separation (Yassa et al., 2011; Kassab and Alexandre et al., 2018), which enables the encoding and retrieval of unique memories (separate engrams).

Also, these associative processes also expand to connecting spatial and temporal components to memory engrams (Hölscher et al., 2003). Interestingly, it has been suggested that left and the right MTL mediate different forms of material specific information processing, mainly depending on the pattern of language dominance (Helmstaedter et al., 1994), with the dominant hemisphere mostly involved in verbal memory, and the non-dominant hemisphere mediating mostly visuospatial memory processes.

The initial storage of engrams is followed by a consolidation process, that starts immediately after learning (Walker et al., 2003). When consolidating a memory, the brain selects the important information that needs to be stored and dispatches this information to longer term storage. Consolidation processes can be measured in performance change between an initial learning performance and a recall performance. Recently, numerous experiments have shown how sleep and memory consolidation are related (Stickgold et al., 2005; Rasch et al., 2007; Walker and Stickgold et al., 2004). Explicit memory consolidation relies greatly on the communication between hippocampal and neocortical areas during sleep (Marshall et al., 2007; Wang et al., 2010). Sleep spindling and slow wave activity represents this communication (Fogel et al., 2006). According to the two-stage model of declarative memory consolidation (Buzsáki et al.,1989), newly acquired memory traces are temporally stored in the hippocampus, followed by a transfer to more stable neocortical stores during the first sleep that follows the initial learning. This transfer is thought to be related to the synchronizing characteristics of slow wave activity (SWA) during sleep (Walker et al., 2004; Marshall and Born, 2007; Diekelmann et al., 2009) and a replay of the newly acquired and temporally stored information, in the form of thalamo-cortical sleep spindles (Wilson et al., 1994; Nádasdy et al., 1999). There is growing evidence that such sleep spindling activity in humans has an important role in memory consolidation (Schabus et al., 2004, Clemens et al., 2005).

Evidence supporting the role of sleep in memory consolidation has been continuously growing in the past years. SWA and sleep spindles are strong indicators of overnight memory consolidation processes in the healthy population (Marshall and Born et al., 2007), however, for example, this pattern seems to be less straightforward for patients with temporal lobe epilepsy (TLE) (Deak et al., 2011, Sarkis et al., 2016), suggesting that such interrelation is mostly true for healthy individuals. Furthermore, sleep loss results in impairment of the PFC, enhancing problems with learning, and sleep loss itself results in the lack of consolidation (Curcio et al., 2006).

5. Interactive memory processes (competing and overlapping processes)

Overlap in cognitive functions reflects a common mechanism, while dissociation means that the two cognitive functions are either independent of each other, or anticorrelate. One way to address the 'competition framework' is to choose a population in which frontal lobe independent cognitive functions are impaired, while implicit sequence learning is intact. A second mode of intervening is to manipulate a common area involved in both executive functioning and implicit learning, - namely the frontal lobe - while an implicit sequence learning task is being conducted. This way one can isolate these two overlapping but different networks in the brain. A third way of looking at competing cognitive functions is through developmental studies, as they can bring insight into the shifts of dominating cognitive functions over healthy and varying development.

As previously mentioned, the frontal lobe, mostly the prefrontal areas and the hippocampus are closely related in the encoding and the consolidation of explicit memories (Eichenbaum et al., 2007, Preston and Eichenbaum et al., 2013). Similarly, the prefrontal area is also important in the encoding of implicit engrams (Rauch et al., 1995; Beldarrain et al., 2002, Pascual Leone et al., 1996), however its exact role is still unclear and remains controversial. Explicit and implicit learning processes can overlap, as well as dissociate, mostly depending on the exact functions involved, the content of the task, as well as intactness of brain areas involved in these processes (Robertson et al., 2007). Interestingly, recent evidence suggests that implicit and explicit learning processes are more flexible than it was previously hypothesized, as the two networks can also compensate for the impairment of one another (Rieckmann et al., 2009, Moody et al., 2004). Even though the fronto-hippocampal projections and the fronto-striato-cerebellar projections differ both functionally, and structurally, still, it is apparent, that the PFC is involved in both trajectories. This common area might explain how the previously mentioned compensation is possible between explicit and implicit processes. Some authors have argued that the PFC is the arbitrary in deciding which learning system is to be activated according to the incoming stimuli (Daw et al., 2005). In the following sections, I will explain through examples how the PFC possibly mediates implicit learning processes, and how it can induce 'communication' between implicit and explicit learning processes.

In a series of experiments, Heindel and colleagues (1989) aimed at pointing out performance differences between patients with different central nervous system disorders (Parkinson's disease – demented and non-demented - PD, Dementia Alzheimer type - DAT,

and patients with Huntington's disease - HD). They concluded that HD patients were found to be impaired on the sequence learning but not the lexical priming task, whereas the DAT patients performed the opposite way. The demented PD patients were found to be impaired on both tests of implicit memory. For both the HD and PD patients, deficits on the sequence learning task correlated significantly with severity of dementia but not with level of primary motor dysfunction. These results show a double dissociation between HD and DAT patients indicating that different forms of implicit memory are dependent upon distinct neuroanatomic systems (sequence learning is mediated by a cortico-striatal system, verbal priming is related to neocortical association areas involved in the storage of semantic knowledge). Importantly, when dementia was present (indicating an additional impairment in the MTL as well) all groups showed impaired implicit learning performance, suggesting that the MTL has a role in implicit learning processes. Additional evidence for a dissociation between priming and sequence learning has been provided by experimental setups comparing college students and elderly adults (Hashtroudi et al. 1991; Schwartz & Hashtroudi et al., 1991), suggesting that the two processes are related to distinct areas in the brain, which is in line with the previous results. Still, it is important to point out here, that in case of severe MTL impairment, sequence learning performance decreased, indicating that in case the healthy balance of 'cognitive fitness' falls over, one can see that implicit learning relies on multiple areas of the brain, including the fronto-striato-cerebellar network, as well as the MTL. A dissociation in MTL and the fronto-striato-cerebellar circuit has been shown in PD patients (Moody et al., 2004) and AD patients as well. For PD patients, the basal ganglia are impaired, resulting in a decrease in implicit sequence learning performance, while leaving explicit learning performance intact. On the other hand, AD patients show a distinct MTL impairment, leading to explicit memory impairments, while leaving implicit learning capabilities intact. Importantly, such clear dissociations are rare to observe in everyday life, as there seems to be a compensatory mechanism between MTL and the fronto-striato-cerebellar circuits (Rieckmann et al., 2009, Moody et al., 2004), and the other way around, implicit learning performance can show alterations when MTL is impaired (Nemeth et al., 2013c).

According to the COVIS ('competition between verbal and implicit systems') theory (Ashby et al., 1998), implicit learning is involved in perceptual categorization (especially if the rule is difficult to verbalize). Ashby and colleagues argue that the caudate nucleus is an important component of the implicit learning system and that the anterior cingulate and prefrontal cortices are critical to the verbal system. According to this theory, abnormalities or

immaturity in the PFC should lead to deficits in categorization tasks in which the optimal rule is verbal. In case the striatum is fully developed and functioning normally, performance should be normal in categorization tasks in which the optimal rule is nonverbal. Evidence from patients with PFC lesions, depressed adults and children support this prediction. Finally, patients with damage to structures that are not part of the COVIS network should show relatively normal category learning.

Janacsek and colleagues tested the developmental pattern of implicit learning capacities, experimentally proving the naive observation that our sequence learning capacities are at their best during childhood and decline over time (Janacsek et al., 2012). One possible reason for this is that frontal areas of the human brain develop ontogenetically the latest, which - according to the competition idea - gives more space to implicit learning mechanisms beforehand. To recap, during childhood the brain is more sensitive to raw probabilities (procedural based tasks), and after the full development of frontal areas it becomes able to adopt more explicit rules (explicit hypothesis testing) as well. A 'competition framework' explains previous experimental results (Janacsek et al. 2012; Nemeth et al., 2013). Similarly, in a series of experiments, Munakata and colleagues defined the three developmental transitions towards a more flexible behavior (Munakata et al., 2012). First, when one's cognitive control is stable enough it can overcome behavioral perpetuations reactively, followed by a proactive development, finally resulting in a type of proactive control that does not rely on environmental signals most of the time and becomes more self-directed. Although developing cognitive control results in many beneficial effects in everyday life, there are also drawbacks. This way, the same group of researchers managed to make a clear distinction between the beneficial effects and drawbacks of high executive functioning: working memory and goal directed behavior benefits from having high executive functioning capacities but disturbs cognitive functioning when conflicting cognitive processes are present, possibly competing for the same cognitive resources (Blackwell et al., 2014).

A great number of implicit category learning studies with additional interfering dual task have shown the phenomena in which attending one task has a certain effect on the performance of the second one (Filoteo et al., 2010, Poldrack et al., 2001). Filoteo and colleagues applied the second task as a dual task paradigm. However, attending a specific task can also induce a competition between certain areas in the brain (Albouy et al., 2008). Interestingly, stress has a similar effect on interacting memory systems. Moderate to high levels of stress leads to more exploitation (rigid habit learning) and less exploration (more flexible

cognitive learning mechanisms), which indicates that the glucocorticoids released during a stressful episode can block flexible cognition (Schwabe et al., 2013). Recent studies suggest that stress expresses cognitive changes through mineralocorticoid receptors (Vodel et al., 2016) resulting in the impairment of executive functions (Shields et al., 2016), as well as episodic memory retrieval (Gagnon et al., 2016). By blocking flexible cognition, our actions remain rigid and automatic, and more prone to ignore changing stimuli from the environment. The relevance of studies aiming at clearing the view of the relationship between certain cognitive functions and the structural/network characteristics they activate/they rely on lies in the fact that this way, one can see these functions not only as encapsulated entities, but as ones that relate to each other and have effects on one another. Hypnosis has been proven to be effective in this manner due to the reversible changes it initiates in cognitive processing (Raz et al. 2002; Egner et al. 2005), in the repression of frontal networks (Kaiser et al. 1997; Kallio et al. 2001; Wagstaff et al. 2007; Fingelkurts et al. 2007; Oakley et al., 2009) and in networks that are responsible for the frontal attentional control and executive systems (Kaiser et al. 1997; Egner et al. 2005; Gruzelier et al., 2006). Nemeth and colleagues used hypnosis as a suitable tool to reduce the competition between frontal lobe related explicit hypothesis testing and striatum related procedural based systems (Nemeth et al., 2013).

In summary, according to the 'competition' framework, fronto-hippocampal and fronto-striato-cerebellar networks can compete for cognitive resources, however if one of the networks are impaired, such competition (Heindel et al., 1989; Moody et al., 2004) can easily turn into cooperation (Rieckmann et al., 2009). This suggests that there is a common, mediating area, deciding which process should be activated (Daw et al., 2005). Also, when this mediating area – the PFC – is overly active or deactivated by experimental manipulation (or is immature), one can see significant changes in implicit learning performance.

6. Extending the neuropsychology of implicit and explicit learning and memory

In the previous sections, structural and functional characteristics and dissociations in implicit and explicit learning and memory have been discussed. To recap, implicit learning mostly relies on the fronto-striato-cerebellar network of the brain, however there is evidence that other brain areas, such as the MTL can compensate when the network is impaired. The SRT has been excessively used as a measure of implicit sequence learning, as it is based on accidental knowledge, without explicit awareness (Howard and Howard et al., 1997; Shanks and St. John et al., 1994). Implicit sequence learning is an extensively researched topic in the

literature of learning and memory, however still some questions regarding overlapping areas remain open: what the role of the PFC is in implicit learning, and how the MTL is related to implicit learning and memory. Also, regarding explicit learning and memory, the related areas include the MTL, also, projections to frontal lobe areas are important in consolidation and recall as well.

In the following I will focus on implicit and explicit learning and memory in three specific disorders: Alcohol Usage Disorder (AUD) Temporal Lobe Epilepsy (TLE) and Autism Spectrum Disorder (ASD). These specific disorders were chosen to be the focus because all three represent a different set of cognitive impairments, therefore it can be very informative to see the overlapping and dissociating aspects of implicit and explicit learning and memory processes. High functioning ASD is characterized by a change in the fronto-striatal network (Langen et al., 2012), thus this patient population can show how this network's alteration can change implicit learning performance. AUD on the other hand is mostly referred to as a disorder resulting in frontal lobe impairments (instead of alterations in the network), causing a distinct deterioration of executive functions (Zinn et al. 2004). In this patient population we can examine whether a distinct impairment in frontal areas results in implicit learning capabilities. TLE is affected by temporal lobe damage and is usually characterized by explicit memory impairments (Frisk and Milner et al., 1990), therefore it can be informative in comparing implicit and explicit memory processes in this population to test the role of the temporal lobe in these processes.

6.1.1. Alcohol Use Disorder (AUD)

The term AUD includes any serious problems with drinking alcohol, resulting in mental and physical health problems (Litrell et al., 2014). Long-term alcohol consumption results in a wide range of behavioral changes, a reduction in overall quality of life, and shows comorbidity with a great number of psychiatric conditions such as eating disorders (Bulik et al., 2004), depression (Grant et al., 1995; Brière et al., 2014), anxiety (Schneier et al., 2010), and substance abuse (Grant et al., 2004). Alcohol has 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 et al. 2004). However, the exact impact of alcohol on implicit cognition is still largely unknown, as most of the experimental data comes from studies using acute alcohol intake, which cannot account for the long-term effects of alcohol dependency. Most of the research on the effects of alcohol consumption on cognition

comes from experiments looking at the acute effects of alcohol intake, however both short- and long-term (chronic) alcohol usages tend to have a temporally stable, but selective effect on implicit and explicit memory processes (Lister et al. 1991; Duka et al. 2001). In the following, I will briefly review research on both short- and long-term effects of alcohol consumption.

Depending on the type of assessment, participants who were under the acute 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 (Duka et al., 2001). A similar study investigated the effects of acute alcohol intake on explicit and implicit false memories using a study list (Garfinkel et al., 2006). In summary, the experiment showed that alcohol decreased semantic activation, which led to a decline in false memories. Increased learning with repetition, which increases the rejection of false memories under placebo, is reversed under alcohol consumption, leading to a decrease in rejection of false memories. The authors argued that this finding was because of an impairment of the monitoring processes during encoding, due to the effects of acute alcohol intake. Kirchner and colleagues examined the effects of alcohol on the controlled and automatic influences on memory performance (2003), with an innovative experimental setup in which they administered the acute alcohol intake before the initial study phase. They used the process-dissociation procedure to investigate the aforementioned effects separately and found that alcohol intake decreased the estimates of controlled contributions, compared to the placebo condition. Also, they found that alcohol intake did not have a significant effect on the rather automatic contributions to the task, thus alcohol impairs performance on an implicit, but conceptually driven task, while leaving the perceptually driven implicit processes intact. Such experimental results are in line with previous literature on the effects of alcohol on executive functions, and frontally driven processes. Binge-drinking has been associated with longer-term memory deficits amongst young adults (Parada et al., 2011). In a study comparing male and female binge drinking and non-binge drinking college students on a verbal memory task, a logical memory task, and a visual explicit memory task, Parada and colleagues found that binge-drinkers performed worse on both the verbal and the logical memory tasks. Unfortunately, the study didn't include a longer follow-up phase, thus the longer effects of binge-drinking are unknown so far. Even though binge-drinking does not count as chronic alcohol use disorder, one can see that if this happens regularly for a long time, it also has detrimental effects on cognition.

Long-term consumption of drugs such as alcohol has been shown to impair explicit recall, while typically induce no effect on priming (Parker, Schoenberg, Schwartz, & Tulving, 1983). Long-term alcohol dependency can result in Korsakoff syndrome, which is a neurological disorder characterized by profound impairments in newly acquired information specific to time and space. Fama and colleagues found deficits in explicit learning in Korsakoff syndrome, meanwhile showing intact implicit learning (2006). These results indicate that while explicit memory processes seem to be impaired by AUD, implicit learning performance is intact in this population, however both studies relied on priming experiments, suggesting that the effects of AUD on other implicit learning processes is still unknown. Long-term alcohol dependency seems to effect sleep and explicit memory consolidation, even after shorter or longer periods of abstinency (Jughanns et al., 2009). Chronic and high alcohol consumption changes sleep patterns (reduces the amount of non-REM sleep), and correlates negatively with performance on a face name association task. The authors conclude that long-term alcohol consumption impairs declarative learning through direct destruction of the frontal lobes, as well as disrupting sleep patterns and therefore impairing memory consolidation. The deterioration found in episodic memory and working memory seems to be a continuous spectrum within alcoholic and Korsakoff-syndrome patients, in which alcohol dependent patients already show a deficit in both working memory (Sullivan et al., 2003) and episodic memory (Pitel et al., 2008).

To sum up, acute alcohol intake and binge drinking results in a decreased integrity of prefrontal areas, inducing problems with mostly executive functions. Furthermore, long-term alcohol intake impairs other areas of the brain as well, including MTL areas, resulting in declarative learning and memory problems. Importantly, previous results indicated that explicit memory processes are impaired, however, implicit learning performance on priming experiments was still intact. The effects of AUD on other implicit learning processes, such as sequence learning processes are still unknown.

6.1.2. Temporal Lobe Epilepsy (TLE)

Temporal lobe epilepsy is the most common form of epilepsy in humans, resulting in ictal and interictal activity of the mesial temporal regions (Engel et al., 2001). This type of epilepsy is often drug-resistant, resulting in a major burden in quality of life for patients (Hermann et al., 2000; Aydemir et al., 2004), and a great concern for epilepsy specialists (Engel et al., 2012). The etiology of temporal lobe epilepsy can be diverse, with hippocampal sclerosis

as one of the leading causes (Wieser et al., 2004). Sclerosis of the hippocampus results in memory decline, TLE of the dominant hemisphere results in verbal memory decline (Frisk and Milner et al., 1990; Saling et al., 1993), while TLE of the non-dominant hemisphere generally impairs the spatial domain of declarative memory (Smith and Milner et al., 1981). Importantly, lesion of both hippocampi results in major memory decline in both spatial and verbal explicit memory domains (Scoville and Milner et al., 1957). Authors argue that this explicit memory loss is due to hippocampal granule cell loss (Pauli et al., 2006).

Nowadays, medical professionals advise choosing surgery over medical treatment in terms of seizure control and improvement of quality of life for TLE patients who are medically difficult to treat, (Wiebe et al., 2001). According to the results of Janszky and colleagues (2005), fMRI predicts (during an explicit visual memory task) memory performance after right MTL epilepsy surgery, as the reduced activation of the MTL region ipsilateral to the epileptogenic region correlates with a favourable postoperative memory performance outcome. Preoperative differences in verbal memory performance and specific patterns of postoperative memory impairments lead to converging evidence that explicit verbal memory relies not only on the MTL, but on a synergistic interaction of temporolateral and MTL regions (Helmstaedter et al., 1997).

Working memory (or short-term storage) is mediated by neocortical temporal structures, whereas long-term consolidation/retrieval is particularly mediated by temporomesial structures. Helmstaedter (1997) argues that the temporomesial system appears to be material nonspecific. However, it is important to keep in mind that although explicit verbal and visual memory processes are lateralized to the left and right MTL (Frisk and Milner et al., 1990) respectively, this lateralization is not always so strict, and different functions within verbal and visual explicit memory are located in different areas raising the question of material specificity, and further differentiating the more simple left and right MTL theory (Saling et al., 2009). On a similar account, Lillywhite and colleagues (Lillywhite et al., 2007) compared three MTL region's structural integrity, activation in these areas and verbal explicit memory performance. They found that verbal arbitrary relational material was most strongly associated to the activation of the left perirhinal cortex. Also, verbal memory recall was related to the activation of the left hippocampus. Their results suggest that the left perirhinal region is responsible for the uptake of arbitrary linkages that underlie new learning, while the hippocampus is important for protecting newly learned information from the effects of interference, suggesting that different

areas of the MTL are responsible for learning new material, as well as protecting this knowledge from forgetting.

TLE has been a basis for examinations of explicit memory paradigms, however the exact role of the MTL in implicit learning processes remains somewhat dim (Leritz et al., 2006). Previous experiments have shown that healthy controls perform superior on a classical eyeblink conditioning experiment (Hermann et al., 2004), amnesic patients with MTL impairment show a decline in performance on a conceptual priming task (Wang et al., 2004), and on a contextual cuing task as well (Chun and Phelps et al., 1999). However, others found impaired explicit memory for left TLE patients with anterior temporal lobectomy, while implicit memory performance remained intact, indicating that implicit learning performance (measured on a verbal memory task) did not rely on left TLE as much as explicit verbal memory performance (Zaidel et al., 1994). Interestingly, they also found a linear relationship between hippocampal cell density (bilaterally) and a better implicit memory performance (stem completion), while on a more explicit part of the task (explicit word recall), patients with anterior temporal lobectomy of the left side performed worse (Zaidel et al., 1994).

According to de Guise and colleagues, frontal and temporal epileptic patients differ in explicit and implicit learning setups (de Guise et al., 1999). In their experiment, they looked at the callosal and the cortical contribution to implicit learning with acallosal and callosotomozed patients with epilepsy in an SRT task. They found that patients with frontal lobe epilepsy (FLE) showed a better explicit knowledge of the procedure but a poorer implicit learning of the task, compared to TLE patients, indicating that implicit learning processes are impaired in TLE. It is important to note however, that patients in this experiment were all acallosal or callosotomized thus the TLE and FLE comparison shown here should only be taken as evidence with caution. Importantly, this is the only study that aimed to investigate implicit sequence learning in the TLE population.

Sleep related SWA and sleep spindles are strongly related to memory consolidation processes in the healthy population, however this pattern is somewhat altered for patients with TLE (Deak et al., 2011, Sarkis et al., 2016). Ictal and interictal epileptic discharges of the medio-temporal region both have a great role in the memory decline visible in TLE, as these discharges interfere with the normal physiological activities of the brain. Interictal spiking increases with sleep depth (Malow et al., 1998), interfering with physiological oscillations such as sleep spindles. Furthermore, there is evidence in feline generalized penicillin epilepsy, that spike and wave discharges are pathological transformations of sleep spindles (Kostopoulos et

al., 2000), however such a direct relationship between temporal spikes and sleep spindles have not been observed so far. Importantly, epileptic discharges appear more often during sleep, eroding physiological sleep patterns and memory consolidation (Parisi et al., 2010; Sarkis et al., 2016; van Schalkwijk et al., 2018). Seizure occurrence can differ between individuals, and though less often compared to frontal lobe epilepsy, nocturnal seizures can appear for some with TLE (Herman et al., 2001; Bernasconi et al., 1998), further altering overnight memory consolidation processes. To our knowledge, know study has investigated sleep related changes in consolidation of implicit sequence learning in the TLE population.

In summary, TLE patients usually show an impairment in either the verbal or the visual (or in both) explicit memory domain, which in part depends on seizure frequency as well as on the years spent with epilepsy syndrome. As the MTL seems to have a role in implicit learning processes as well (possibly in binding information and adding contextual associations), investigating whether this type of learning is impaired in this population can be very informative in specifying the role of the MTL in implicit learning. Importantly, to the best of my knowledge, no study has yet investigated implicit sequence learning capabilities in TLE only (without any other neurological disorders present).

6.1.3. Autism Spectrum Disorder (ASD)

Individuals on the ASD spectrum are often hypersensitive to sensory stimuli, and present at least two types of symptoms: problems in social communication and interaction, and restricted, repetitive patterns of behavior, interests or activities. Long term issues may include difficulties in performing daily tasks, creating and keeping relationships, and maintaining a job (Comer et al., 2016). Cognitive impairments of children with ASD increase during development (Rosenthal et al., 2013), and can also be related to lower structural and functional cortical connectivity among the affected regions (Hollander et al., 2005; Just et al., 2007; Muller et al., 2004). Previous studies also found increased striatal volume in ASD compared to typically developing children (TD) (Hollander et al., 2005; Muller et al., 2004).

As mentioned before, the striatal region of the brain has a key role in procedural learning processes. Over the past decade, a great number of studies have focused on implicit sequence learning in ASD. Implicit, nonconscious learning of sequences involving the fronto-striatal network seems to be intact or even better in ASD children compared to TD children (Barnes et al., 2008; Foti et al., 2015; Nemeth et al. 2010b; 2013). Similarly, others showed that the process

of implicit sequence learning seems rather intact in children with ASD (Nemeth et al., 2010b; Brown et al., 2010), however the method how they acquire such skills is limited compared to healthy controls (Gordon et al., 2007). Gordon and colleagues found that ASD children require more practice, and perform better with a shorter, 4 element sequence, compared to an 8-element sequence. Finally, further supporting evidence comes from a meta-analysis (Foti et al., 2015) comparing studies using the classical or alternating version of SRT. This review of previous literature points to relatively intact or even superior performance in implicit learning paradigms in the ASD population compared to healthy individuals. Other studies have also found relatively intact explicit learning in ASD children, and impairment of explicit learning in lower functioning ASD children in both recognition and cued recall tasks (Boucher et al., 2012). In summary, implicit learning of sequences seems to be intact in children with ASD to some extent, depending very much on the difficulty of the task, as well as the level of functioning.

Studies focusing on explicit sequence learning show a rather dissociating pattern between ASD and TD children. Importantly, in a previous research, Mostofsky and colleagues found contradictory evidence arguing that there is a deficit in implicit learning of children and adolescents with ASD, possibly due to cerebellar dysfunction (Mostofsky et al., 2000), highlighting some importance of the cerebellum in implicit learning. The authors conclude that deficits in implicit learning may contribute to the cognitive and behavioral pattern of ASD. On the other hand, Travers and colleagues (2010) concluded that the performance of ASD and TD adolescents is very similar in the SRT task. They used a modified version of the SRT task, including a 12-element sequence to measure motor learning in individuals with ASD (average functioning and high functioning autistic adolescents). In a later fMRI experiment using the SRT task as well, Travers and colleagues (Travers et al., 2015) found that individuals with ASD showed decreased activation in the right superior parietal lobule (SPL) and right precuneus during learning, which suggests that a decrease in parietal lobe activation does not impact implicit learning capabilities. Others found decreased connectivity and decreased cerebellar activity in children with ASD during sequence learning (Mostofsky et al., 2009), however activation patterns in subcortical regions such as the basal ganglia did not differ between healthy individuals and people with ASD in a set of similar learning tasks (Brambilla et al., 2003), indicating that the basal ganglia is crucial in implicit learning processes.

Changes in the fronto-striatal network of ASD children are well researched, however, others found alterations in other brain areas as well, such as the MTL or the cerebellum. Goh and colleagues (Goh et al., 2012) reviewed a great number of neuroimaging studies of ASD

children, performing mostly declarative and procedural learning and memory. According to the literature, the authors concluded that abnormalities of hippocampal subregions may also contribute to autistic deficits in episodic and relational memory; disturbances to an amygdala-based network may contribute to autistic deficits in socio-emotional learning and memory; and abnormalities of the striatum may contribute to developmental dyspraxia in individuals with ASD.

High functioning ASD and TD children perform similarly on a word learning task, however, children with ASD tend to remember the phonological features of words better, while TD children remember both phonological and semantical characteristics of words (Norbury et al., 2010). Importantly, the two groups significantly differed in delayed recall performance, which the authors concluded as a deficit in the semantic portion of learning, as well as frequently reported sleep disturbances in ASD children. In a more recent review, Ullmann and colleagues (2015) focused on the intact cognitive functions instead of the impairments in a wide range of neuro-denegerative and psychiatric disorders. In their study, they found that compared to other cognitive functions, such as executive functions, declarative learning and memory function is still rather intact, suggesting that this function can compensate the impairments of other functions to a certain extent.

To sum up, increasing evidence suggests that ASD children show intact implicit learning abilities on most experimental setups, however their performance differs in the strategy they use (Renner et al., 2000; Janacsek and Nemeth et al., 2013), as well as according to the extent of certain brain areas involved in these processes. The pervious experiments mainly focused on either implicit or explicit task setups with ASD children, however shifting the rate of awareness has not been tested before in this patient population. Our experiments aimed at testing the hypothesis whether ASD children show intact or even superior implicit learning compared to TD children, as well as how explicit shifts in the same task will alter these results to see the overlap between the two learning and memory processes in this population.

7. Research questions and hypotheses

In order to have a better understanding of the specific brain areas involved in implicit and explicit learning and memory processes and how they can possibly overlap, we chose to look at multiple populations, as well as multiple cognitive functions in relation to implicit and explicit learning paradigms.

Our first experimental population included adults with alcohol-dependency and matched healthy controls. In this experiment, we wanted to take a closer look at the competition between executive functions and implicit learning processes. 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 this 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, as a second hypothesis, 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 on executive functions requiring different but partly overlapping neurocognitive networks.

Our second experimental population included patients with TLE, and matched healthy controls. In this experiment, we aimed at taking a closer look at the role of the MTL in implicit learning processes. According to the literature, there is evidence that the MTL is related to implicit memory processes, especially early in acquisition, presumably relating to contextual and relational information. Here we hypothesized that if MTL plays any role in implicit learning processes, then we should find some kind of impairment in implicit sequence learning in TLE patients compared to healthy controls. Also, we were interested to see whether any difference emerges in consolidation of implicitly acquired knowledge between the TLE patients and healthy controls, as this question has not been investigated before.

The third study also included TLE patients. We aimed to have a closer look at how the pathologic relationship between sleep and memory in TLE effects explicit memory processes including acquisition, as well as consolidation. We hypothesized that sleep spindles have a role is memory consolidation of TLE patients as well, however we assumed that TLE has a modulatory effect of learning on sleep spindles. Also, we wanted to see how the slow and fast subdivision of sleep spindles relates to learning and memory consolidation in TLE. Our analysis focused on both trait and state-like effects of sleep spindles on learning and memory consolidation, furthermore on the possible long-term consequences of epilepsy on learning and memory consolidation.

Our fourth experimental population included children with ASD and matched healthy controls. This study aimed to contribute to a better understanding of the implicit learning capabilities of children with ASD and to further explore explicit alterations within implicit

learning processes. Our first hypothesis was that implicit sequence learning performance of ASD children will be intact or even superior compared to TD children. In case ASD children have difficulties in explicit processes, we predict that explicit shifts in the same task will alter these results by impairing performance of the ASD group compared to the TD group. Our experimental design enables us to take a closer look at whether previous results showing intact implicit sequence learning in the ASD population in fact point to intact implicit learning or intact sequence learning in general.

Materials and methods

Study I. Comparing frontal lobe functions and implicit sequence learning in AUD patients and healthy controls

Description of this study is based on previously published research [1]

Participants

Fourteen alcoholic patients (11 males/3 females) and 16 controls (11 males/5 females) participated in the experiment. The alcohol-dependent and the control groups were matched on age, gender and years of education (Table 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 3 weeks prior to the experiment. History of participant's alcohol dependency was diverse, still, according to the number of relapses all participants have had at least one relapse (the mean of total relapses: 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 behaviour and were not taking any psychoactive medications. All participants provided signed informed consent agreements and received no financial compensation for their participation.

[1] 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.

Variables	Control Group		Alcohol Usage Disorder Group		*p-value*
	Mean	SD	Mean	SD	
Age	49.56	10.68	48.5	10.68	0.788
Education	2.12	0.72	2.07	0.83	0.851
Digit Span Task	6.27	0.9	5.86	1.03	0.301
Listening Span Task	3.86	0.83	3.11	0.69	0.021
Counting Span Task	4.15	0.94	3.44	0.98	0.08
Letter Fluency Task	20.82	5.29	14.78	4.76	0.006

Table 1. Participant's group (Control versus Alcohol Usage Disorder (AUD)), age, and education. Years spent with education are grouped into 4 categories: 1: elementary school, 2: high school without graduation, 3: finished high school with graduation, 4: higher academic education. Mean and standard deviation of performance on executive function tasks, such as Digit Span Task, Listening Span Task, Counting Span Task and Letter Fluency Task are listed.

Tasks

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 (Howard and Howard 1997). In this task, a stimulus (a dog's head) appears in one of the four empty circles on the screen and participants are instructed to press the corresponding button as fast and accurately as they can. The original procedure includes a stimulus (a dog's head), which appears in one of four horizontally arranged empty circles on a computer screen (Nemeth et al., 2010). Participants were instructed to press the button that corresponds to the actual location of the stimulus, as fast and as accurate as possible. The computer was equipped with a special keyboard, which only contained four heightened keys (Z, C, B, M on a QWERTY keyboard) necessary for responding. These keys correspond to the target circles appearing on the computer screen. Stimuli were presented in blocks of 85 stimuli, from which the first five button presses were random and served practice purposes only. Practice trials were followed by an alternating sequence, which included 8 elements (e.g., 2r4r3r1r, where numbers represent the four circles shown on the screen, and r represents the random elements between the target elements). This sequence was repeated ten times in a block. Due to the structure of the sequences in the ASRT task, some triplets or runs of three consecutive elements (events) occur more frequently (high frequency triplets) than others (low-frequency triplets; Figure 2). For example, in the above illustration, 2_4, 4_3, 3_1, and 1_2 (where "_" indicates the middle element of the triplet) would occur often because the third element (italic numbers) could be derived from the sequence or could also be a random element.

In contrast, 2_3 or 2_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 thus more predictable from the initial event when compared to the low-frequency triplets [also known as non-adjacent second-order dependency (Remillard et al., 2008). Therefore, before analysing 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 (43, 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 trials are low frequency triplets. Similar to previous studies using the same task (Nemeth et al., 2010, Howard and Howard et al., 1997, 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 (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. Previous studies have also 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 et al., 1997, Howard et al., 2004). In addition, general skill learning – namely the general increase in speed of responses throughout the task, irrespectively of the triplet types – can also be measured in the ASRT task.

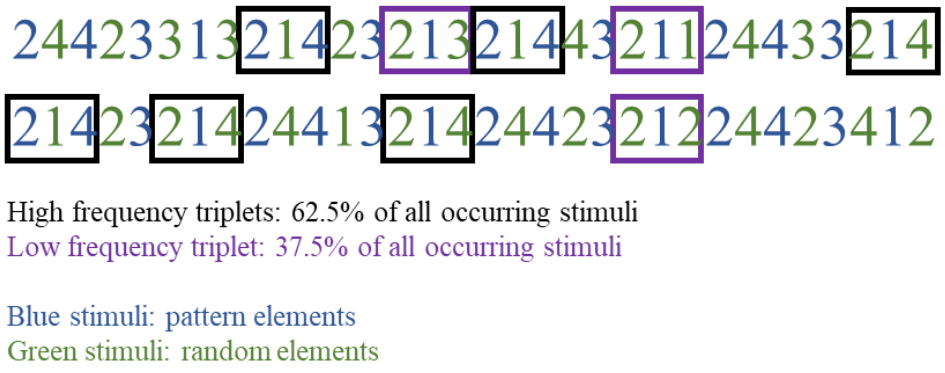

Figure 2. Illustration of the stimulus stream in the ASRT task. The task contains an alternating sequence structure (e.g, 2r4r3r1r, where numbers correspond to the four locations on the screen and the r represents randomly chosen locations), thus some runs of three consecutive elements (called triplets) occur more frequently than others.

Here, we were interested in implicit sequence learning, as well as general skill learning—general speedup in the task, irrespective of the triplet types—was also measured in

the task. In this version of the ASRT task, participants did not know about the underlying sequence. The instruction of the task was for participants to be as fast and as accurate as possible. 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 Task

The Digit Span Task (Isaacs and Vargha-Khadem 1989; for Hungarian version see Racsmány et al. 2005) is a measure of phonological working memory (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 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 single digit, e.g., 6).

Listening Span Task

The Listening Span Task (Daneman and Blennerhassett 1984; for Hungarian version, see Janacsek et al. 2009) is a widely used complex working memory test. 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 Task

The Counting Span Task (Case et al. 1982; Engle et al. 1999; Conway et al. 2005; for the Hungarian version see Fekete et al., 2010) is a complex working memory task lacking a strong verbal component. Each trial included three to nine blue circles as targets and 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 2 to 6. 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 (Spreen and Strauss 1991; for Hungarian version, see Tanczos et al. 2014a, b) is a widely used task to measure the central executive component of the working memory model (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 s, without repetitions, synonyms or generated forms of the same word, and 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 min. 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 s 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

As mentioned in previous analyses (Bennett et al. 2007; Barnes et al. 2008) blocks of ASRT were organized into epochs of five blocks. The first epoch contains blocks 1–5, and the second blocks 6–10, etc. As participants' accuracy remained very high throughout the test similar 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-frequency 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-frequency and low-frequency triplets.

As we wanted to see a more consistent role of executive functions in relation to implicit learning processes, we calculated a composite score out of all tasks measuring executive functions in this experiment. First, we transformed performance on the listening span task, the counting span and the letter fluency tasks into z scores, then we used an average of the transformed data as a composite executive function 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, analysis including executive functions were run on a restricted sample only (control group: n = 11, alcohol-dependent group: n = 14).

To compare learning between healthy controls and AUD patients, we first conducted a mixed design ANOVA with TRIPLET (high versus low) and EPOCH (1-5) as within-subject factors and GROUP (control versus AUD) as a between-subject factor. In a different mixed design ANOVA analysis, exploring the relationship between executive functions and implicit learning, we added EXECUTIVE GROUP (low versus high) as a between subject factor, and TRIPLET (high versus low) as a within subject factor. Furthermore, we analysed the within subject effect of TRIPLET (high versus low) by adding both between subject factors: PATIENT GROUP (AUD versus control) and EXECUTIVE GROUP (high versus low). Planned comparisons and post-hoc analyses were conducted by Fisher's LSD pairwise comparisons.

Study II. Implicit sequence learning and consolidation in TLE

Participants

Twelve TLE patients, and 12 age and gender matched healthy controls were included in the present study (Table 2). Healthy controls were chosen from the staff of the hospital, years spent in education were slightly higher for this group. Experiments were performed in the Epilepsy Monitoring Unit (EMU) of the National Institute of Clinical Neurosciences in Budapest. Patients had been referred to the EMU for video-EEG monitoring as part of complex pre-surgical epileptological evaluation with the possibility of a future resective surgery to

remove the seizure onset zone. This evaluation method included a standard 10-20 scalp-electrophysiological examination methods, and a more invasive, so called 'foramen ovale' electrode. This electrode is referred to as semi-invasive, as it is surgically inserted via the foramen ovale, goes under the brain reaching the surface of the temporal lobe's perirhinal cortex. In this experiment, we only analysed behavioural data, therefore electrophysiological methods and results will not be discussed.

group	age	gender	education
TLE	40	1.66	2.33
control	39.83	1.75	3.08

Table 2. Participant's group, gender, age, and education. Group 1 is patients with TLE, Group 2 is matched healthy controls. Gender: 1 male, 2: female. Years spent with education are grouped into 4 categories: 1: elementary school, 2: high school without graduation, 3: finished high school with graduation, 4: higher academic education.

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 1997b). For the current version of the ASRT task, 20 experimental blocks (including 10 repetitions of the 8-element sequence containing alternating random and sequence stimuli) were organized into 4 epochs in each session. We decided to make the task shorter for the TLE patients so that they remain more motivated throughout the task in both sessions. This way, the task lasted for about 20-25 minutes at each session.

Statistical analysis

As previously mentioned in the experiments listed above, blocks of ASRT were organized into epochs of five blocks. As participants' accuracy remained very high throughout the test similar 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-frequency 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-frequency and low-frequency triplets.

We were also interested in a more detailed analysis of the learning process, therefore we separately analysed the first and second halves of each block. The so called "halfblock"

analysis was first described by Nemeth and colleagues (2013) in a similar study setup measuring sequence specific learning in MCI patients, where they observed sequence learning deficit in patients with MCI compared to controls. They argued that by splitting blocks into two halves, one can get a more fine-grained analysis of the data and the specific mechanisms behind the development of sequence representations (Nemeth et al., 2013; Gamble et al., 2014).

To compare learning between healthy controls and TLE patients, we first conducted a mixed design ANOVA for with TRIPLET (high versus low) and EPOCH (1-8) and HALFBLOCK (first versus second part of each block) as within-subject factors, and GROUP (control versus TLE) as a between-subject factor. Planned comparisons and post-hoc analyses (when needed) were conducted by Fisher's LSD pairwise comparisons. To measure consolidation between Session 1 and Session 2, we first conducted a mixed design ANOVA with TRIPLET (high versus low) and BLOCK (blocks 19–20 from Session 1 versus blocks 1–2 from Session 2, instead of the last epoch of the first session compared to the first epoch of the second session, 2-2 blocks were compared to have a better view of the consolidation process) and HALFBLOCK (first versus second part of each block) as within-subject factors and GROUP (TLE versus control group) as a between subject factor.

Study III. Explicit learning and sleep related consolidation in TLE

Participants

Twenty TLE patients were included in the present study. Experiments were performed in the Epilepsy Monitoring Unit (EMU) of the National Institute of Clinical Neurosciences in Budapest. Patients had been referred to the EMU for video-EEG monitoring as part of complex pre-surgical epileptological evaluation with the possibility of a future resective surgery to remove the seizure onset zone. Prior to the video-monitoring, all participants conducted a detailed neuropsychological evaluation, according to the 'temporal lobe protocol' of the institute. For more details about participants, see Table 3.

pat	sex	Age	years spent with TLE	benzo	IQ	medication	neuropsychological deficit	verbal/visual memory deficit	side of epilepsy	structural/functional deficits
1	f	30	21	no	98	mono	mild	both	right	concordant right
2	m	40	9	yes	na.	poly	moderate	both	left	concordant left
3	f	41	8	yes	88	poly	mild	none	right	none
4	f	39	24	yes	64	poly	severe	mostly verbal	left	concordant left
5	f	42	9	yes	122	poly	mild/none	none	na.	na.
6	m	30	29	yes	110	poly	mild	mostly visual	right	concordant right
7	m	31	7	no	109	mono	mild	mostly visual	right	concordant right
8	f	29	11	no	106	mono	mild/none	verbal/none	left	concordant left
9	m	55	22	yes	121	poly	mild	verbal	na.	na.
10	f	50	49	no	82	mono	moderate	both	left	concordant left
11	m	68	47	yes	na.	poly	severe	both	right	concordant right
12	f	69	12	no	121	mono	mild	verbal/none	left	concordant left
13	m	39	12	yes	73	poly	moderate	verbal	left	concordant left
14	m	26	13	yes	93	poly	mild	visual	right	concordant right
15	f	71	17	yes	na.	poly	none	none	right	na.
16	m	35	9	no	na.	mono	moderate	verbal	left	concordant left
17	f	23	13	no	111	mono	mild	mostly verbal	left	concordant left
18	f	31	28	no	82	mono	moderate	mostly verbal	left	concordant left
19	f	26	14	yes	92	poly	moderate	both	bitemp	bitemporal
20	f	47	35	no	91	mono	severe	both	bitemp	bitemporal

Table 3. Participant's sex, age, years spent with TLE and IQ, data on benzodiazepine medication at the time of the experiment, possible neuropsychological deficits, and side of epilepsy. Both structural and functional data were taken into consideration to specify the side of epilepsy.

EEG recording

EEG was conducted by a standard 10-20 positioned 32 channel recording. All recorded evenings with detected seizures were excluded from further analysis. Signals were collected, prefiltered (0.33–1500 Hz, 40 dB/decade anti-aliasing hardware input filter), amplified and digitized with a synchronous sampling rate with 12-bit resolution by using a 28 channel EEG/polysystem (Brain-Quick BQ 132S, Micromed, Italy), including bipolar electrooculogram, electromyogram and electrocardiogram electrodes. A further 40 dB/decade anti-aliasing digital filter was applied by digital signal processing which low-pass filtered the data at 450 Hz. Finally, the digitized and filtered EEG was down sampled at 512-1024 Hz. All recordings were re-referenced to a linked mastoid reference. The following electrodes were used for later analysis: Fp1, Fp2, F3, F7, F4, F8, C3, C4, T3, T4, P3, P4, T5, T6, O1, O2. Sleep stages were manually detected according to established guidelines (Rechtschaffen et al., 1968), as wake S1, S2, S3, S4 and REM. Artefact rejection was manually performed in 4s long epochs.

For descriptive measures of the macrostructure of sleep, see Table 4, for relative time spent in sleep stages see Table 5. Multiple learning events and sleep recordings provided us with a within and a between subject design at the same time, thus we were able to detect individual learning and consolidation patterns, as well as more general effects of sleep on learning and consolidation. We calculated an average score for all learning and consolidation scores, as well as for sleep spindle parameters, collapsed over all three learning nights.

Sleep spindle detection

First, we conducted an FFT analysis for all evenings, followed by an individual averaging of the spectral powers. In the following, we compared the power of all frequency bins between 9-16 Hz (in bins of 0.25), with average learning and consolidation performance with the Pearson correlation method. To rule out the effect of possibly extreme data points and outliers, we filtered our data 25-75% around the median based on previous recommendations (Leys et al., 2013). Filtering took place in all frequency bins for all channels separately, thus we managed to save as many data points as possible. Possible confounding factors of multiple comparisons were corrected according to the Rüger area method (Simor et al., 2013; Bódizs et al., 2014; Ujma et al., 2016). This method determines significant areas in both the spatial and the frequency domain. If $p < 0.05/2$ ($p < 0.025$) for at least 50% of significant results, or if $p < 0.05/3$ ($p < 0.016$) for at least 33% of significant results within an area, then the area is considered statistically significant. In the FFT analysis, the area of significance extends from the first frequency bin in which a statistical test is significant on any electrode, until the last frequency bin in which a statistical test is significant on any electrode. Also, areas of significance had to last for at least 4 frequency bins (1 Hz). A second analysis included the previously mentioned FFT analysis, with the exception that we divided the frequency ranges to a slow and a fast frequency range, between 8-12 and 12-16 Hz respectively. Power spectrum was averaged for both slow and a fast frequency ranges, resulting in a more robust data set.

Peak sleep spindle frequencies were calculated with an individually adjusted method (IAM) by evaluating each sleep spindle in the recording and defining average slow and fast frequency ranges (Ujma et al., 2015). Spindle peak frequencies, spindle numbers, durations, amplitudes were calculated automatically in every channel for both slow and fast spindles separately This sleep spindle detection method takes into account both inter-individual variations and intra-individual consistency in sleep spindle frequency (De Gennaro et al., 2005, 2008), analysing sleep spindles at the individual peak frequency for all subjects. The analysis consists of six fix steps. First, the program calculates an average amplitude spectrum with an

FFT between 8-16 Hz (1). This is followed by the individual adjustment of the frequency limits of slow and fast sleep spindles (2.). The program then detects the individual-specific spindle middle frequencies (3.). Individually adjusted, derivation specific amplitude criteria are added for sleep spindles (4). EEG is filtered (FFT based Gaussian windows) and smoothed (by a moving average weighted Hanning window) (5). Table 2. The previously mentioned threshold (step number 4) is used for the detection and characterization of sleep spindles (6). Number, duration, amplitude of slow and fast sleep spindles in all recorded channels were calculated by this method. Further details of the IAM method can be found in (Bódizs et al., 2009; Ujma et al., 2015).

Pat	Sleep duration*	Sleep efficiency **	nREM duration	S1 duration	S2 duration	S3+S4 duration	REM duration	S1 duration	S2 duration	S3+S4 duration	REM duration	# of sleep cycles***
1	375.33	58.59	288	53.22	107.22	127.56	87.33	53.22	107.22	127.56	87.33	5
2	311.87	48.68	257.54	47.11	96.77	113.64	54.33	47.11	96.77	113.64	54.33	4
3	366.43	61.41	299.77	73.44	119.11	107.22	66.66	73.44	119.11	107.22	66.66	4
4	388.22	53.91	279.66	104	120.44	55.22	108.55	104	120.44	55.22	108.55	4.67
5	337.67	52.7	260.89	72.55	109.11	79.22	76.78	72.55	109.11	79.22	76.78	3.33
6	402.78	62.87	328	111.22	140.78	76	74.78	111.22	140.78	76	74.78	5.33
7	329.44	51.42	240.89	82	94.78	64.11	88.56	82	94.78	64.11	88.56	3.67
8	354.5	55.33	276.67	42.33	121.33	113	77.83	42.33	121.33	113	77.83	4
9	400.44	62.5	389.56	173.67	105.67	110.22	10.89	173.67	105.67	110.22	10.89	1.67
10	352.44	55.01	294	170.78	87.66	35.55	58.44	170.78	87.66	35.55	58.44	2
11	445.84	69.59	384.17	170.5	119.67	94	61.67	170.5	119.67	94	61.67	4
12	369.84	57.73	275	100.67	119.84	54.5	94.83	100.67	119.84	54.5	94.83	3
13	286	44.65	215.84	75.17	65	75.67	70.17	75.17	65	75.67	70.17	4
14	334.89	52.27	264.78	57.11	142	65.67	70.11	57.11	142	65.67	70.11	3.67
15	368.89	57.58	310	117.44	93.78	98.78	58.89	117.44	93.78	98.78	58.89	4.33
16	393.56	61.43	337.22	59.33	155.33	122.55	56.33	59.33	155.33	122.55	56.33	1.67
17	408.11	46.91	304.22	42.33	136.34	125.56	103.89	42.33	136.34	125.56	103.89	5.67
18	256	39.96	224.44	43.44	55.67	125.33	31.56	43.44	55.67	125.33	31.56	3
19	410	63.99	340	90.33	132.33	117.33	70	90.33	132.33	117.33	70	4.33
20	435.67	69.15	387.89	97.89	205.44	84.55	47.78	97.89	205.44	84.55	47.78	3.33
average	366.396	56.284	297.927	89.2265	116.4135	92.284	68.469	89.2265	116.4135	92.284	68.469	3.7335

Table 4. Macrostructure of sleep in average and for each participant is listed. Note: *minutes, **%, ***REM periods.

Pat	Relative nREM duration*	Relative S1 duration	Relative S2 duration	Relative S3+S4 duration	Relative REM duration
1	77.83	14.95	27.68	35.2	22.17
2	82.58	14.49	32.82	35.27	17.41
3	81.58	19.28	32.44	29.85	18.41
4	71.61	26.6	30.56	14.44	28.38
5	76.92	21.47	31.86	23.6	23.08
6	82.71	27.52	36.9	18.29	17.29
7	74.02	25.56	29.06	19.41	25.98
8	78.16	30.44	34.01	31.88	21.83
9	97.21	43.08	26.47	27.65	2.79
10	83.99	48.7	25.26	10.03	16
11	86.03	38.14	26.95	20.94	13.98
12	74.5	27.3	32.38	14.82	25.51
13	75.44	26.11	22.7	26.64	24.56
14	79.64	17.24	43.54	18.86	20.36
15	84.07	31.76	25.56	26.75	15.93
16	86.11	15.55	39.9	30.66	13.89
17	74.34	10.32	33.32	30.7	25.66
18	87.76	16.85	20.76	50.15	12.24
19	83.9	24.03	32.44	27.43	16.1
20	89.31	22.97	47.47	18.87	10.69
average	81.3855	25.118	31.604	25.572	18.613

Table 5. Macrostructure of relative time spent in sleep stages for each participant is listed.

Finally, we compared absolute numbers of slow and fast sleep spindles with learning and consolidation scores in two analyses. First, we compared absolute spindle numbers with the consecutive nights learning performance and the following morning's consolidation performance. We also averaged absolute spindle numbers, and learning and consolidation performance over all learning events, similarly to how we did in the previous analyses.

Task

To measure declarative learning, we administered a modified version of the Rey Verbal Auditory Learning Task (RAVLT) (Rey et al., 1964; for Hungarian version see Kónya et al., 1995). Testing was administered on two to three consecutive evenings, depending on the amount of time the patient spent in the EMU. We used a modified version of the original RAVLT task, creating three equally balanced lists of words (A, B and C lists) for multiple testing events. Also, we skipped the interference word list to avoid cognitive overload and added a second delayed recall to the following morning to measure overnight consolidation. The task consisted of five rounds of word-list learning. The word-lists were composed of fifteen nouns selected evenly in length and frequency of occurrence. All words were read out five times by the experimental assistant. The task was to repeat as many words as possible out of the 15

nouns after each learning round. Initial learning was followed by a delayed recall 30 minutes later to measure encoding, and a second recall the following morning to measure the long-term retention of encoded items.

Statistical analysis

Multiple learning events and sleep recordings provided us with a within and a between subject design at the same time, thus we were able to detect individual learning and consolidation patterns, as well as more general effects of sleep on learning and consolidation. We calculated an average score for all learning and consolidation scores, as well as for power spectrum, and individual sleep spindle parameters for density, duration and amplitude of sleep spindles, collapsed over all three nights. Collapsing of the data was important, as we wanted to see whether there is a trait like-effect of sleep spindles on learning skills and consolidation capabilities.

Pearson correlation was used to explore possible trait-like effects of sleep spindles on learning and memory consolidation. Furthermore, we z-normalized learning and consolidation scores to have an individual average learning score for each patient, to see night-to-night changes. This led us to have an individualized view of the relationship between one's sleep spindle parameters, learning and consolidation. To explore the relationship between state-like sleep spindle characteristics and memory performance, we used Pearson correlation to correlate the z-normalized learning scores with sleep spindle indices to see whether individual changes in performance can be assigned to changes in sleep spindle characteristics. Also, we calculated the relationship between the years spent with TLE and IQ with sleep spindle parameters, controlling for benzodiazepines, and age as well. Finally, we looked at possible effects of the macrostructure of sleep on learning and consolidation performance, by correlating averaged absolute and relative time per sleep stage with learning scores and average consolidation gain with the Pearson correlation method. Following the analysis with the IAM detection, we also conducted correlation analyses with the bin-wise FFT data and the more robust, slow and fast spindle frequency range averaged FFT data.

Study IV. Implicit sequence learning and consolidation in ASD and the role of explicit instructions

Description of this study is based on previously published research [2]

Participants

Fourteen children with Autism Spectrum Disorder (ASD) and fourteen age and IQ-matched typically developing (TD) controls participated in the experiment (Table 6). Children with ASD were recruited from the University of Szeged, Faculty of Medicine, Department of Psychiatry, and from public schools in Szeged and neighbouring settlements. Children with ASD had been previously diagnosed by trained psychiatrists from the University of Szeged, Faculty of Medicine, Department of Psychiatry. ASD children were all recruited from already existing patient population of specialists. TD children were recruited from public schools in Szeged and from schools in neighbouring settlements. Importantly, TD children did not show any kind of significant learning difficulty, did not suffer from any psychiatric or relevant somatic condition. Informed written parental consent and verbal assent of both ASD and TD children were obtained, participants did not receive financial compensation for their participation.

Group	Age	IQ	Listening Span Task	Counting Span Task	Digit Span Task
ASD	11 (3.11)	105.84 (27.82)	2.27 (0.76)	2.87 (0.92)	4.61 (1.10)
TD	12 (2.74)	108.61 (17.68)	2.99 (1.07)	3.38 (1.05)	5.08 (1.18)

Table 6. ASD and TD participant's age, IQ, and performance on the Listening Span Task, the Counting Span Task and the Digit Span Task.

Alternating Serial Reaction time Task (ASRT)

Sequence learning was measured by an altered version of the ASRT task (Howard and Howard et al., 1997 (for more details concerning the alternation, see Figure 2A). For the current

[2] Virag, M., Janacsek, K., Balogh-Szabo, V., Chezan, J., & Nemeth, D. (2017). Procedural learning and its consolidation in autism spectrum disorder. *Ideggyógyászati szemle*, 70(3-4), 79-87.

version of the ASRT task, blocks were organized into explicit and implicit blocks (Figure 3B): Blocks 1–2, 10–11 and 19–20 were implicit, while Blocks 3–9 and 12–18 were explicit (Song et al., 2007a; Nemeth et al., 2010). In the implicit (uncued probe) blocks, participants were informed that the main aim of this task was to find out how extended practice affects performance on a simple reaction time task and all stimuli appear in a random order in the task. In the instructions we emphasized performing the task as fast and as accurately as they could. In the explicit (cued experimental) blocks of the task, the regularity was marked by different stimuli for sequence and random elements (Song et al., 2007a). 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 3A). Participants were informed that penguins always had randomly chosen locations while dogs always followed a predetermined order (part of the pattern). Children were instructed to find the pattern defined by the dogs in order to improve their performance, thus, to be faster and more accurate using this sequence information to predict the sequence elements. This way we were able to detect the effects of changes in the instruction on the task performance.

Procedure

A learning phase (Session 1) was followed by a testing phase (Session 2), separated by a 16-hour interval period. The first session was in the afternoon, between 2 and 4 PM, and took approximately 30–35 minutes. The second session was administered the next morning, between 7 and 9 AM, and lasted for a similar time interval. Importantly, all participants were instructed to aim for a good night of sleep between the two sessions, and to avoid all distracting activities between the two sessions.

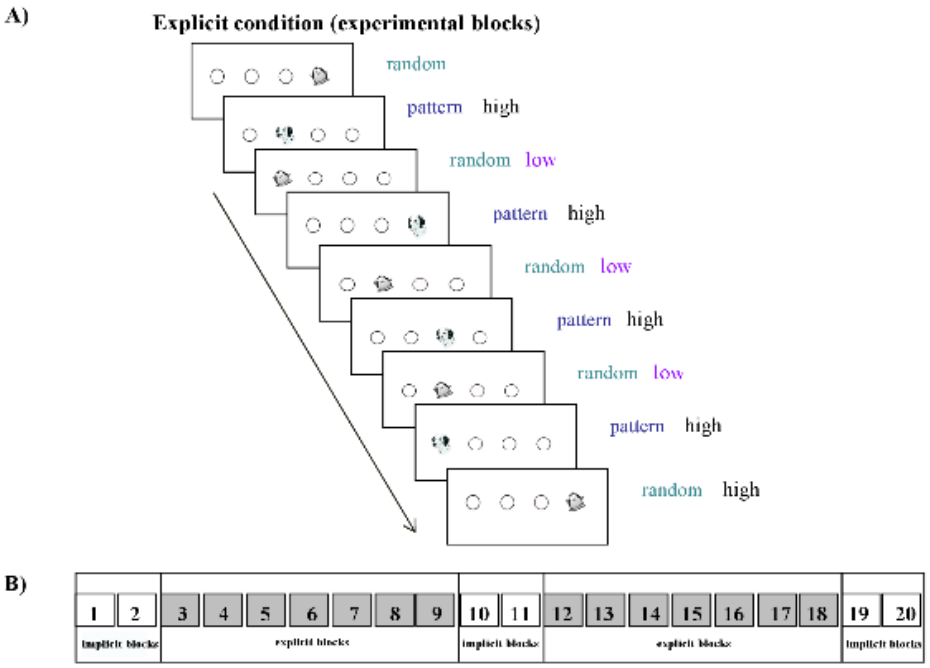

Figure 3. Design of the study. An explicit version of the ASRT task was administered (A) with additional probe blocks (B). The first session consisted of 20 blocks (probe and explicit alternating), the second session (administered 16 hours later during the next morning) consisted of 9 blocks.

Statistical analysis

To compare learning between TD and ASD groups, we first conducted a mixed design ANOVA for the explicit blocks with TRIPLET (high versus low) and BLOCK (3–9; 12–18) as within-subject factors, and GROUP (ASD versus TD) as a between-subject factor. For the implicit blocks we also applied a repeated measures ANOVA with TRIPLET (high versus low) and BLOCK (1–2; 10–11; 19–20) as within-subject factors and GROUP (ASD versus TD) as a between-subject factor. Planned comparisons and post-hoc analyses (when needed) were conducted by Fisher's LSD pairwise comparisons. To measure consolidation between Session 1 and Session 2, we first conducted a mixed design ANOVA with TRIPLET (high versus low) and BLOCK (blocks 19–20 from Session 1 versus blocks 1–2 from Session 2) as within-subject factors and GROUP (ASD versus TD) as a between subject factor for the probe blocks. To measure consolidation in the explicit blocks, we applied a mixed design ANOVA with TRIPLET (high versus low) and BLOCK (12–18 from Session 1 versus 3–9 from Session 2) as

within-subject factors and GROUP (ASD versus TD) as a between-subject factor. Finally, a more fine-grained analysis was also conducted using a mixed design ANOVA with TRIPLET (high versus low), BLOCK (blocks 3–9; 12–18 for the explicit condition and blocks 1–2; 10–11; 19–20 for the implicit condition) and HALFBLOCK (first and second part of each block) as within-subject factors and GROUP (ASD versus TD) as a between-subject factor.

Results

Study I. Comparing frontal lobe functions and implicit learning in AUD patients and healthy controls

Implicit sequence learning and executive function performance in alcohol usage disorder patients and matched healthy controls

To compare sequence learning between the groups, RTs were analysed 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. 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 × 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 groups in sequence specific learning (Figure 4). 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 patients and healthy controls did not differ significantly. 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 × 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 on general skill learning.

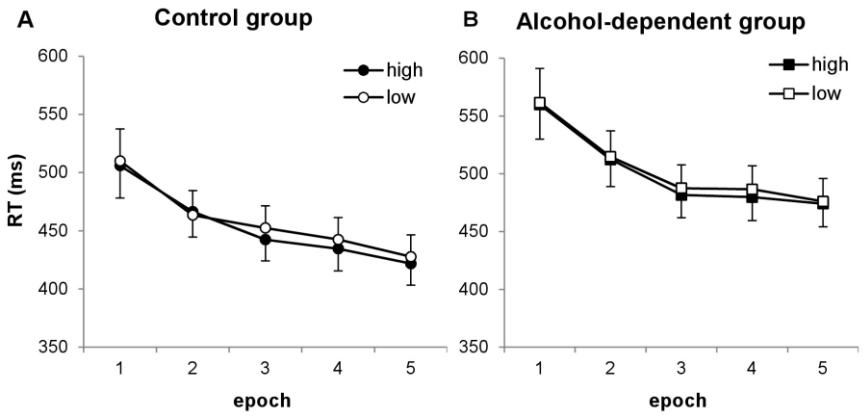

Figure 4. Reaction times (RTs) in the ASRT task for the control (a) and the alcohol-dependent groups (b). There was no difference between the two groups either in sequence specific learning (RT difference between high-frequency and low-frequency triplets) or in general skill learning (overall RT improvement 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 × EXECUTIVE GROUP interaction showed a strong trend toward significance ($F(1, 21) = 3.988$, $\eta p\ 2 = 0.160$, $p = 0.059$), 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) (Figure 5.). 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.

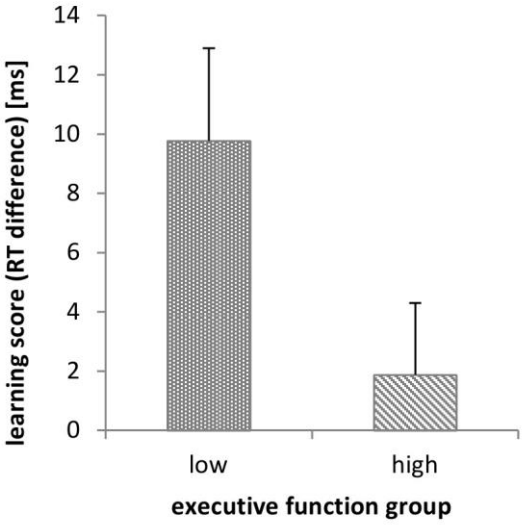

Figure 5. Interaction between sequence specific learning scores and the level of executive functioning. Distinct columns represent patients separated by levels of executive functioning (low versus high).

Relationship and possible modulating factors 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 controls 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 groups were analysed together (Figure 6a). Within-group correlations showed similarly moderate, negative correlation in the control group ($r(11) = -0.499$, $p = 0.118$; Figure 6b) and a relatively strong negative correlation in the alcohol dependent group ($r(14) = -0.635$, $p = 0.015$; Figure 6c). 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.

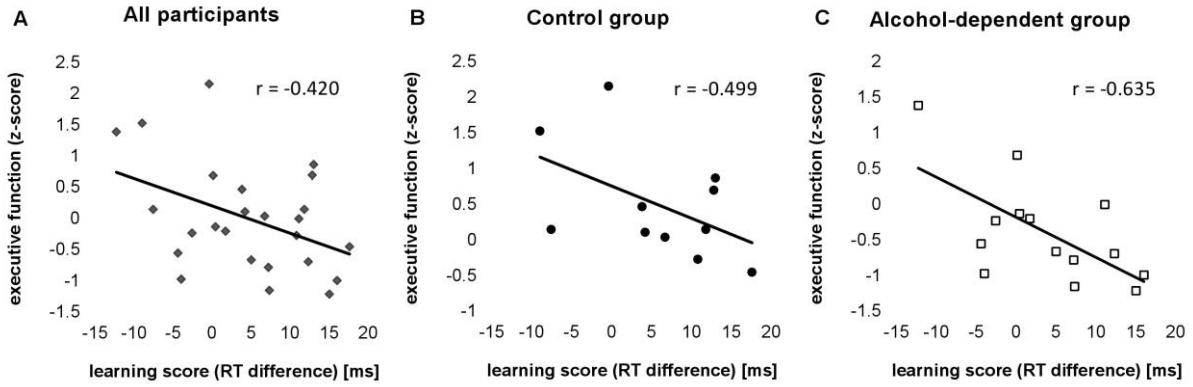

Figure 6. Relationship between sequence-specific learning and executive functions. There was a moderate to strong negative correlation between these measures for all participants (a), as well as in the controls (b) and alcohol-dependent group (c) separately. Thus, weaker executive functions correlated with better sequence-specific learning performance.

Study II. Implicit sequence learning and consolidation in TLE

Implicit sequence learning performance in TLE patients and matched healthy controls

We collapsed all 8 epochs (session 1 and session 2) to see whether TLE patients and healthy controls managed to acquire sequence specific knowledge in the task. Overall, participants managed to acquire sequence-specific knowledge (the main effect of TRIPLET: $F(1, 23) = 64.555$; $p<0.001$). However, the ANOVA revealed significant differences in sequence-specific learning between the TLE group and matched healthy control participants (significant TRIPLET*GROUP interaction: $F(1, 23)=7.358$, $p=0.013$). Overall, the control group showed greater sequence specific learning compared to the TLE patients (14.69 sec vs. 7.27 sec, respectively). The main effect of EPOCH was also significant ($F(1, 23)=36.098$, $p<0.001$), indicating that participants showed general speed-up during the task, irrespectively of triplet types. Additionally, neither the EPOCH*GROUP ($F(1, 23)=0.124$; $p=0.738$), nor the TRIPLET*EPOCH*GROUP ($F(1, 23) = 0.001$; $p=0.973$) interaction reached significance, suggesting that the rate of general speed-up and the dynamics of learning was similar in the two groups (Figure 7).

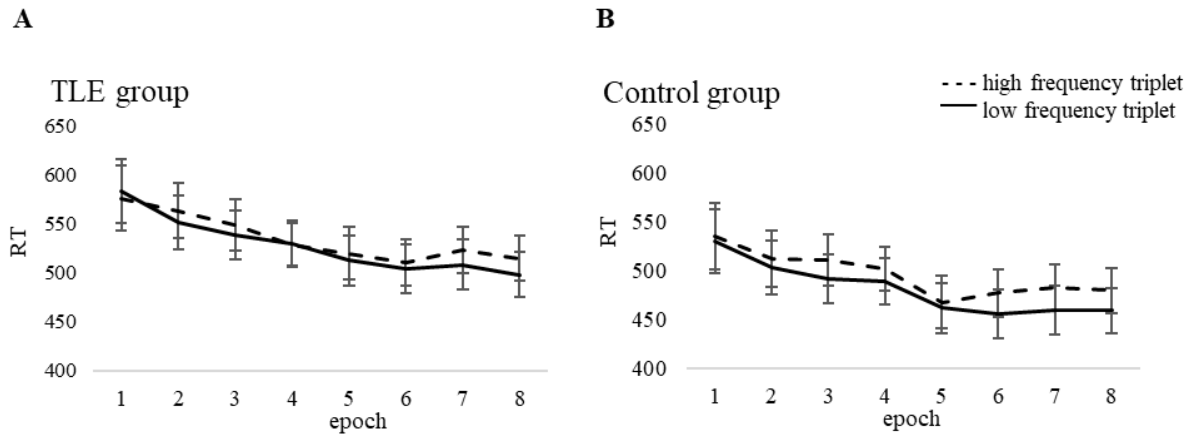

Figure 7. Sequence specific learning in TLE (A) and matched healthy control group (B) over 8 epochs. Separate lines indicate high and low triplets, difference between reaction time (RT) to distinct triplets reflects sequence specific learning. Error bars represent standard error of the means.

Difference in performance during the first and the second half of the experimental blocks

Again, we looked at performance in the 8 epochs together (session 1 and session 2), further dividing each block into two to see possible within-block differences in performance. The ANOVA revealed significant differences between the first and second halves of the blocks (TRIPLET*HALFBLOCK: $F(1, 23)=4.087$, $p=0.05$). Furthermore, the two groups differed in

this effect, indicated by the significant TRIPLET*HALFBLOCK*GROUP interaction (F(1, 23)=5.231, p=0.032): the control group showed greater sequence-specific knowledge in the second halves of the blocks than in the first halves, while the TLE group's sequence-specific knowledge was similar in the two halves of the blocks (Figure 8).

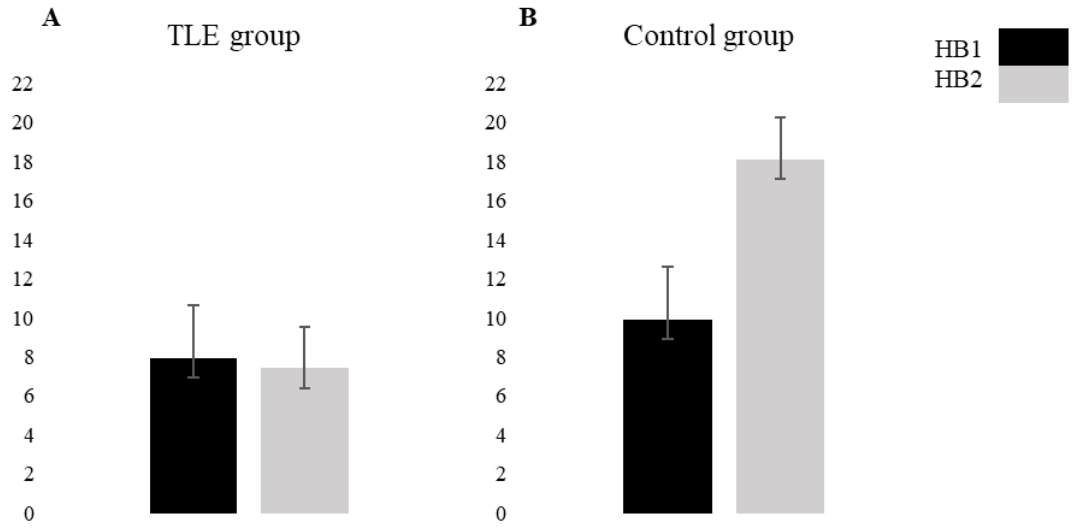

Figure 8. Sequence learning performance of TLE (A) and matched control group (B). Separate columns indicate performance in the first and the second half of blocks (HB1 and HB2, respectively). Error bars represent standard error of the means.

Consolidation of implicit sequence learning in TLE and matched healthy controls

Analysis of consolidation effects between Session 1 and Session 2 showed that participants did not show forgetting of the sequence, indicated by the significant difference in the main effect of TRIPLET (F(1, 23)=14.616, p=0.001), and the lack of significant differences between the two sessions (TRIPLET*EPOCH interaction: F(1, 23)=0.009, p=0.923). The main effect of EPOCH was significant (F(1, 23)=7.591, p=0.012), which suggests that participants showed an offline general speed-up in performance, irrespective of the group (EPOCH*GROUP interaction: F(1, 23)=0.899; p=0.353). This was also true for sequence-specific learning, as there was no significant difference between the two groups in this manner (TRIPLET*EPOCH*GROUP F(1, 23)=2.673, p=0.116), indicating that both the TLE and the control groups retained the acquired triplet knowledge over the offline period (Figure 9).

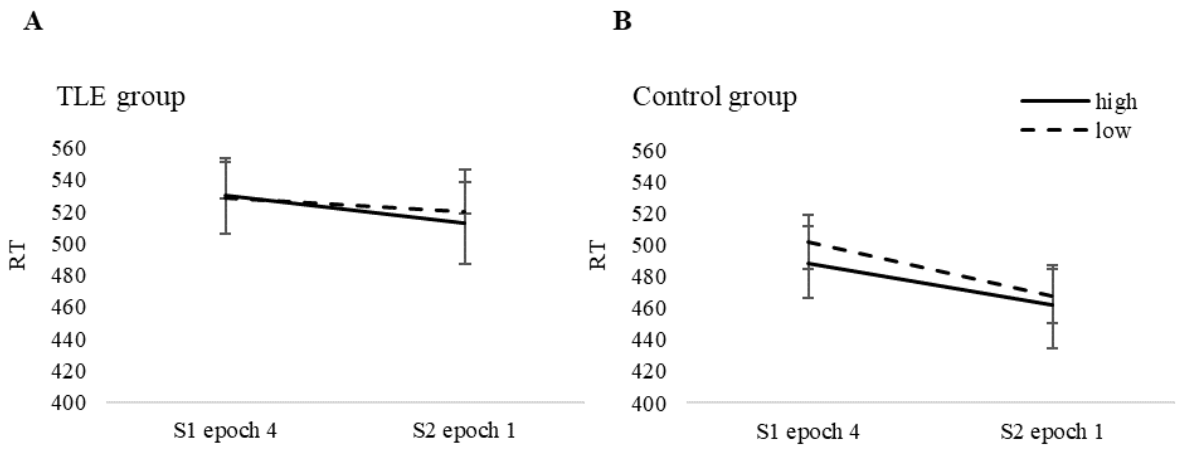

Figure 9. Consolidation between Session 1 and Session 2 in TLE (A) and matched healthy control (B) groups. Error bars represent standard error of the means.

Within-block position effects in the consolidation of implicit sequence learning in TLE and matched healthy controls

We were also curious to see whether performance on the first and the second halves of the blocks shows different consolidation. The ANOVA suggested that participants did not show forgetting of the sequence, irrespective of within-block position effects (TRIPLET*HALFBLOCK interaction ($F(1, 23)=0.199$, $p=0.660$; TRIPLET*EPOCH*HALFBLOCK interaction: $F(1, 23)=1.042$, $p=0.319$). The EPOCH*HALFBLOCK interaction did not reach significance either ($F(1, 23)=2.010$, $p=0.170$), which suggests that offline changes in average RTs (general speed-up) were similar in the first and second halves of the blocks. This remained true irrespective of the group (EPOCH*GROUP*HALFBLOCK interaction: $F(1, 23)=0.005$; $p=0.943$). This was also true for sequence-specific learning, as there was no significant difference between the two groups in this manner (TRIPLET*EPOCH*GROUP*HALFBLOCK $F(1, 23)=1.555$, $p=0.266$), indicating that participants did not show forgetting between session 1 and session 2, irrespective of whether the first or second halves of the blocks were tested (Figure 10).

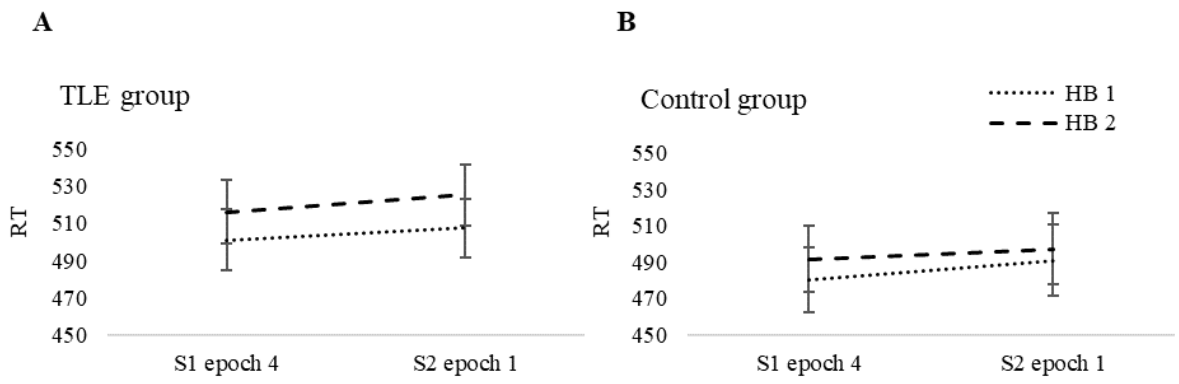

Figure 10. Consolidation between Session 1 and Session 2 in TLE (A) and matched healthy control (B) groups. Distinct lines indicate the first and the second halves of the blocks. Error bars represent standard error of the means.

Study III. Explicit learning and sleep related consolidation in TLE

Learning and memory performance of TLE patients

Average learning performance of participants followed a classical learning curve (Fig 1.), showing increased learning with multiple learning rounds. On average, participants showed a decline in memory retention after 30 minutes, which on average was followed by either retention of the learned amount of words or a minimal amount of forgetting. The learning curve of participants showed that the learning capabilities of patients with TLE fall short from that of healthy individuals, as a maximal learning performance was rare amongst participants. Only three out of twenty participants showed maximal learning performance, also, such performance was only present for one learning occasion out of the three, for all three participants. We calculated an individual average for each spindle parameter by adding all learning nights into the analysis, to see whether there is an individually stable trait effect of sleep spindles on learning performance and overnight consolidation. We excluded one patient due to problems with the EEG recordings (Figure 11).

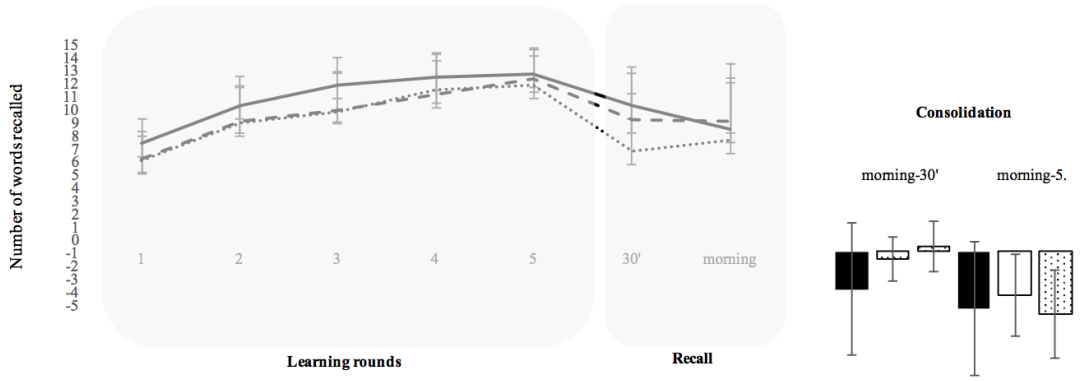

Figure 11. Average learning and overnight consolidation performance in the modified version of the Rey verbal learning task (learning rounds 1-5; delayed recall, morning recall). Distinct lines refer to the average performance of the three learning events.

Overall, the number of words recalled per learning rounds showed a negative relationship with the years spent with epilepsy syndrome (Rey 1: r=-0,59; p=0,007, Rey 2: r=-0,59; p=0,007, Rey 3: r=-0,52; p=0,02, Rey 4: r=-0,66; p=0,002, Rey 5: r=-0,55; p=0,013). To the contrary, years spent in education correlated positively with performance on almost all learning rounds (Rey 1: r=0,45; p=0,058, Rey 2: r=0,5; p=0,032, Rey 3: r=0,57; p=0,013, Rey 4: r=0,54; p=0,019, Rey 5: r=0,47; p= 0,046). Not surprisingly, we found a positive relationship between IQ and the number of words recalled per learning rounds, which was most well-marked in the first three learning rounds. Also, we found negative correlations between slow and fast

sleep spindle density, duration and years spent with epilepsy syndrome at multiple electrode sites.

Relationship between sleep spindle measurements, explicit learning and memory consolidation in TLE

The FFT analysis of the average sleep and learning data showed a significant correlation between faster sleep spindle frequency bins (between 12,75 Hz and 13,75 Hz) and memory consolidation. After the Rüger area correction, correlations remained significant at p<0,05/2:50% at the T3-T4-C3-C4-P3-P4-O1-T6 area; and p<0,05/3:25% at the T4-C4-P3-P4 area, at 13,5 Hz (Figure 12.). Correlations reached significance between 12,75 and 13,75 Hz, however correlations only outlived Rüger area corrections at 13,5 Hz, which is certainly at the fast spindle frequency range.

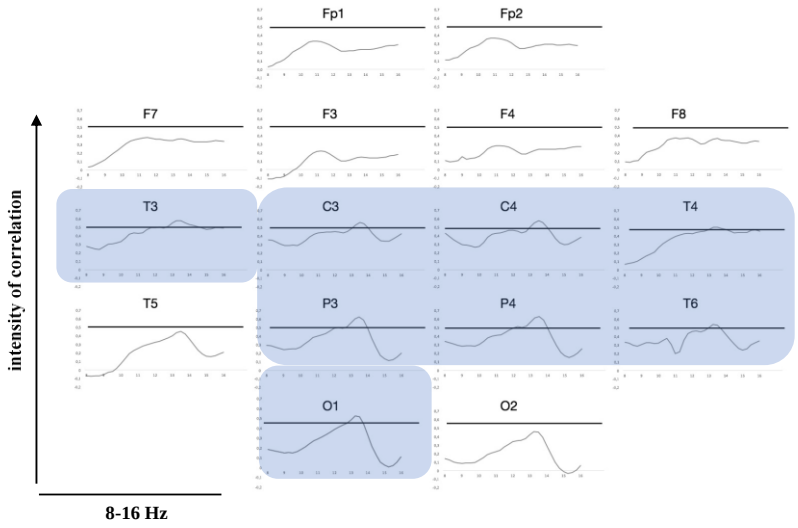

Figure 12. Spectro-correlogram of memory consolidation performance and FFT power between 8 and 16 Hz (by 0,25 Hz bins). The x axis represents frequency between 1-16 Hz, the y axis shows the Pearson correlation coefficient between consolidation gain and relative EEG power in the given frequency bins. Solid, horizontal lines represent the critical partial correlation coefficient (p=0.05).

In order to get data on different spindle parameters underlying these results, we used the IAM method for detailing spindle characteristics. Average number of words recalled per learning round correlated with the average slow spindle density (Figure 13.,), and slow spindle duration (Figure 14.) on various electrode sites, indicating a trait-like relationship between slow spindle density, duration and learning performance in the TLE population. Following the Rüger

area correction, slow spindle density correlations at F8 and T4 electrode sites remained significant at p<0,05/2: 66%, p<0,05/3: 0% at the second learning round, indicating that these results do not outlive a more rigorous cutoff. Importantly, at the third and fourth learning round, only correlations at F8 electrode survived the correction at the less rigorous cutoff. Correlations between slow spindle duration and learning outlived the corrections with the following parameters: p<0,05/2: 81% at Fp1-Fp2-F7-F8-T3-T4-T5-T6-O2 electrode sites; p<0,05/3: 36% at Fp1-Fp2-F8-T4-T5 electrode sites during the second learning round, p<0,05/2: 58% Fp2-F4-F8-T4-T5 electrode sites; and p<0,05/3: 8% at F8 during the third learning round. Significant correlations between slow spindle duration and learning performance during the fourth and fifth learning round didn't survive any of the corrections.

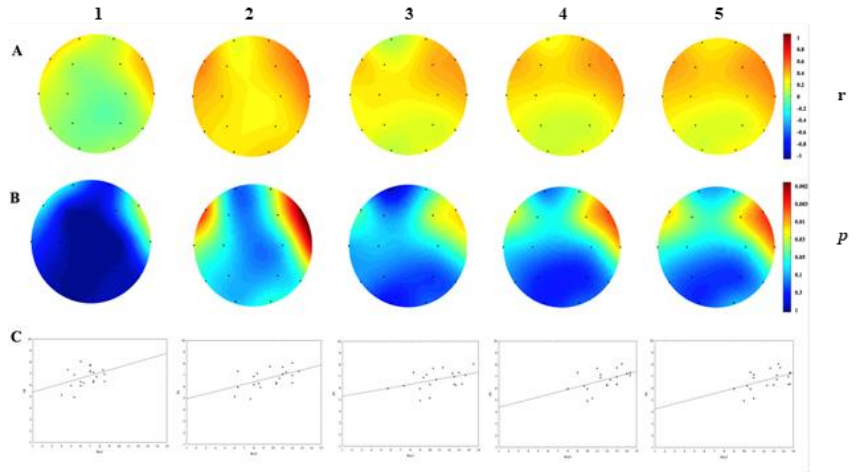

Figure 13. Correlation between slow spindle density and learning performance of the five learning rounds. The first row represents the correlation coefficients, the second row shows significance levels. The third row shows the scatterplot of the correlations.

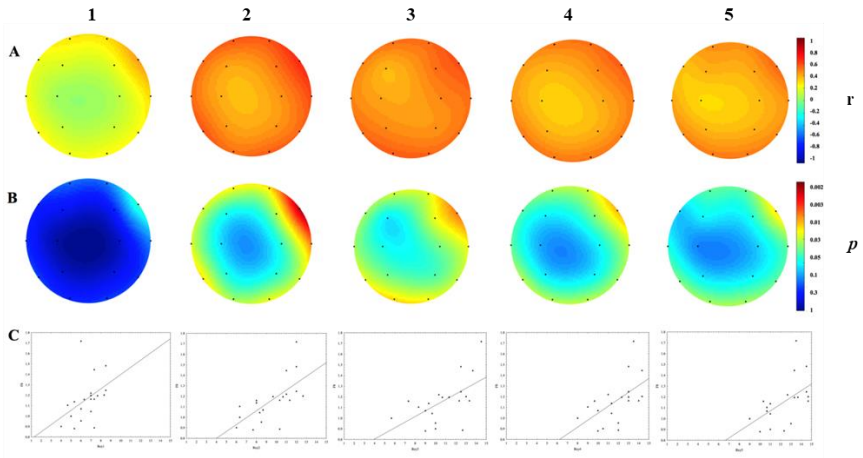

Figure 14. Correlation between slow spindle duration and learning performance of the five learning rounds. The first row represents the correlation coefficients, the second row shows significance levels. The third row shows the scatterplot of the correlations.

Average overnight consolidation showed a positive correlation with average slow spindle amplitude at electrode sites at the right hemisphere (F4, P4, T4) (Figure 15.), Rüger area corrected at p<0,05/2: 100% at F4, P4, T4 electrode sites; and p<0,05/3: 0%, indicating that correlations only remain stable at the less rigorous cutoff. Also, we found a positive correlation between average fast sleep spindle density (Figure 16.) and average consolidation at multiple electrode sites, Rüger area corrected at p<0,05/2: 50% at Fp1-Fp2-F7-F4-C3-T4-P3 electrode sites; and p<0,05/3: 16% at F4-T4 electrode sites.

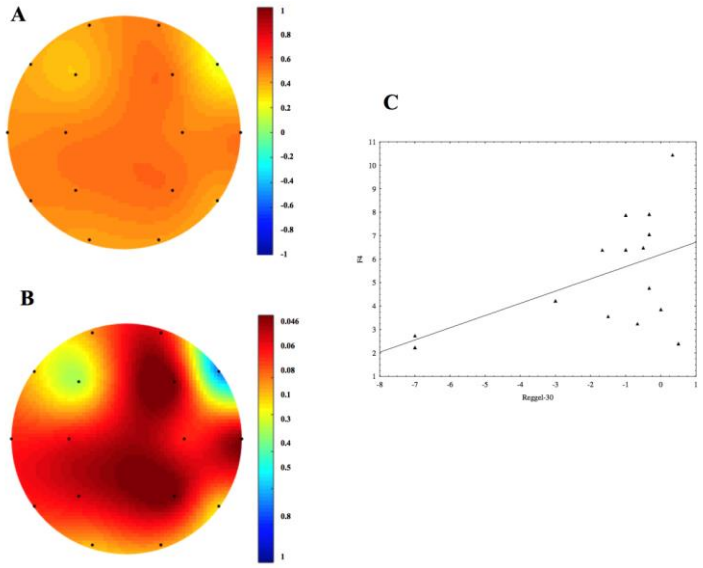

Figure 15. Correlation between average slow spindle amplitude and average overnight consolidation. A represents the correlation coefficients, B shows significance levels, C shows the scatterplot of the correlation

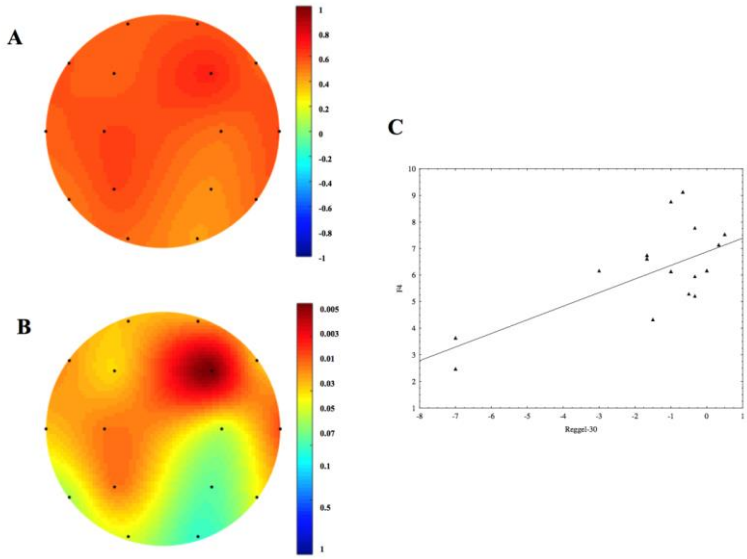

Figure 16. Correlation between average fast spindle density and average overnight consolidation. A represents the correlation coefficients, B shows significance levels, C shows the scatterplot of the correlation

These results are in line with the results of classical FFT method, in which spectral power in the fast spindle frequency range correlated with memory consolidation on similar electrode sites. However, the IAM method detected a relationship between sleep spindle and initial learning performance, which was not visible with the FFT analysis. We argue that the partial overlap between the IAM method and the standard FFT is due to the characteristics of the IAM method, which calculates an individually adjusted frequency range for slow and fast sleep spindles respectively, and in the later analyses, only these frequency ranges are taken into the analyses. This way, we could add individually adjusted spectral powers of slow and fast spindle characteristics, eliminating distorting effects of the standard deviation of spectral powers. The average frequency range was between 10.94 Hz and 12.05 Hz for slow, and between 13.08 Hz and 14.33 Hz for fast spindles. Standard deviation was 0.85 Hz for the slow spindle frequency range, and 0.64 Hz for the fast, indicating that even though frequency ranges were in line with the standard sleep spindle frequency ranges, there was a relatively large variance in slow and fast frequency ranges between patients.

If we analyzed the state-like effect between consolidation gain and normalized spindle parameters, we found positive correlations between slow spindle density (temporal and parietal electrode sites), fast spindle density (frontal electrode sites), fast spindle duration (frontal electrode sites), however these correlations did not reach significance. Absolute sleep spindle numbers showed a significant positive relationship with memory consolidation at Fp1-Fp2-F4-F8 electrode sites. Importantly, this correlation was only present when single evenings were correlated with memory performance, indicating a state-like relationship between the number of sleep spindles and memory consolidation. We argue that the partial overlap between the IAM method and the standard FFT is due to the characteristics of the IAM method, which calculates an individually adjusted frequency range for slow and fast sleep spindles respectively, and in the later analyses, only these frequency ranges are taken into the analyses. This way, we could add individually adjusted spectral powers of slow and fast spindle characteristics, eliminating distorting effects of the standard deviation of spectral powers. The average frequency range was between 10,94 Hz and 12,05 Hz for slow, and between 13,08 Hz and 14,33 Hz for fast spindles. Standard deviation was 0,85 Hz for the slow spindle frequency range, and 0,64 Hz for the fast, indicating that even though frequency ranges were in line with the standard sleep spindle frequency ranges, the relatively large standard deviation between patients.

Possible effects of the macrostructure of sleep on learning performance and consolidation was also in our focus, thus we correlated learning and memory consolidation scores with the macrostructural indexes of sleep. Our indexes included sleep duration, sleep

efficiency, REM and nREM duration, absolute and relative durations of S1-S4 sleep stages. We didn't find any significant correlations between macrostructural parameters and learning or consolidation scores. This suggests that the macrostructure itself does not have a significant effect on learning capacity or consolidation of verbal engrams.

Correlations on the state-like relationship between sleep spindle parameters, learning and consolidation did not show such clear results. Consolidation gain and normalized spindle parameter correlations showed a positive relationship between slow spindle density (temporal and parietal electrode sites), fast spindle density (frontal electrode sites), fast spindle duration (frontal electrode sites), however these correlations did not reach significance.

Study IV. Implicit sequence learning and consolidation in ASD and the role of explicit instructions

Sequence specific learning of the ASD group in probe blocks

The ANOVA showed no significant main effect of TRIPLET ($F(1, 27) = 2.528$, $p = 0.124$) in the probe blocks of Session 1. The TRIPLET*GROUP interaction, however, was significant ($F(1, 27) = 5.113$, $p = 0.032$), suggesting differences in sequence-specific learning between the ASD and the control group (Figure 18A). While the ASD group exhibited significant learning ($p = 0.011$) in that they responded faster to high-frequency triplets compared to the low-frequency ones, the control group did not learn the sequence ($p = 0.639$). In addition, the main effect of BLOCK was also significant ($F(1, 27) = 49.240$, $p< 0.001$): participants showed general speed-up during the task, irrespectively of triplet types. The significant BLOCK*GROUP interaction ($F(1, 27) = 11,967$, $p< 0.001$) suggests differences in general skill learning between the ASD and TD group, with more speed-up for the ASD group. The TRIPLET*BLOCK*GROUP interaction was not significant ($F(1, 27) = 1,545$, $p = 223$).

Sequence specific learning of the ASD group in explicit blocks

Both ASD and TD groups managed to acquire sequence-specific learning in explicit blocks (Figure 18B) as well (main effect of TRIPLET: $F(1, 27) = 11.41$; $p = 0.002$). However, the repeated measures ANOVA revealed no difference in sequence-specific learning between ASD and TD groups in the explicit ASRT blocks of the first session (TRIPLET*GROUP interaction: $F(1, 27) = 0.035$, $p = 0.854$). The main effect of BLOCK was significant ($F(1, 27) = 12.294$, $p = 0.02$), indicating that participants showed general speed-up during the task,

irrespectively of triplet types. Additionally, neither the BLOCK*GROUP (F(1, 27) = 1.958; p = 0.173), nor the TRIPLET*BLOCK*GROUP (F(1, 27) = 2.095; p = 0.160) interaction was significant.

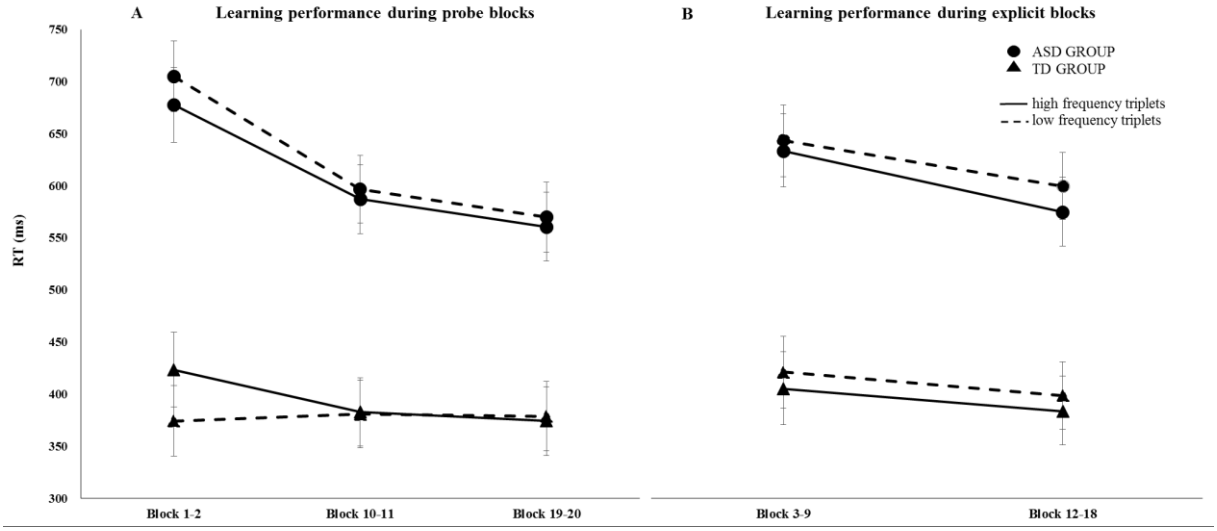

Figure 18. Learning performance in Session 1 of ASD and TD groups in probe (A) and explicit (B) blocks in Session 1. The gap between the solid (high frequency triplets) and the dashed lines (low frequency triplets) indicates sequence-specific learning. Error bars indicate standard error of the means.

Consolidation of sequence specific learning in the ASD and the TD groups

Analysis of consolidation effects between Session 1 and Session 2 showed that participants did not show forgetting of the sequence, indicated by the significant difference in the main effect of TRIPLET (F(1, 27) = 10.908, p = 0.003), and the lack of significant differences between the two sessions (TRIPLET*BLOCK interaction: F(1, 27) = 1.333, p = 0.259). The main effect of BLOCK was not significant (F(1, 27) = 0.668, p = 0.421), which suggests that there was no offline general speed-up, irrespective of triplet types and group (BLOCK*GROUP interaction: F(1, 27) = 0.001; p = 0.988). This was also true for sequence-specific learning, as there was no significant difference between the two groups in this manner (TRIPLET*BLOCK*GROUP F(1, 27) = 2.349, p = 0. 137), indicating that participants did not show forgetting between the Session 1 and Session 2 (Figure 19A) in the probe blocks.

Overall, participants did not forget the sequence during the offline period in the explicit blocks either, indicated by the significant main effect of TRIPLET (F(1, 27) = 15.057, p< 0.001), irrespective of the group (TRIPLET*GROUP interaction F(1, 27) = 0.119, p = 0.733). Thus, learning performance was retained by Session 2 (TRIPLET*BLOCK: F(1, 27)= 2.745, p = 0.110). The main effect of BLOCK was not significant (F(1, 27) = 1,831, p = 0.421), which

suggests that there was no offline general speed-up, regardless of triplet types and group (BLOCK*GROUP interaction: F(1, 27) = 0.068, p = 0.796). Furthermore, this was true for both groups, as there was no significant between the two groups difference in this manner (TRIPLET*BLOCK*GROUP interaction: F(1, 27)= 0.421, p = 0.522), indicating that participants did not show forgetting between the Session 1 and Session 2 (Figure 19B).

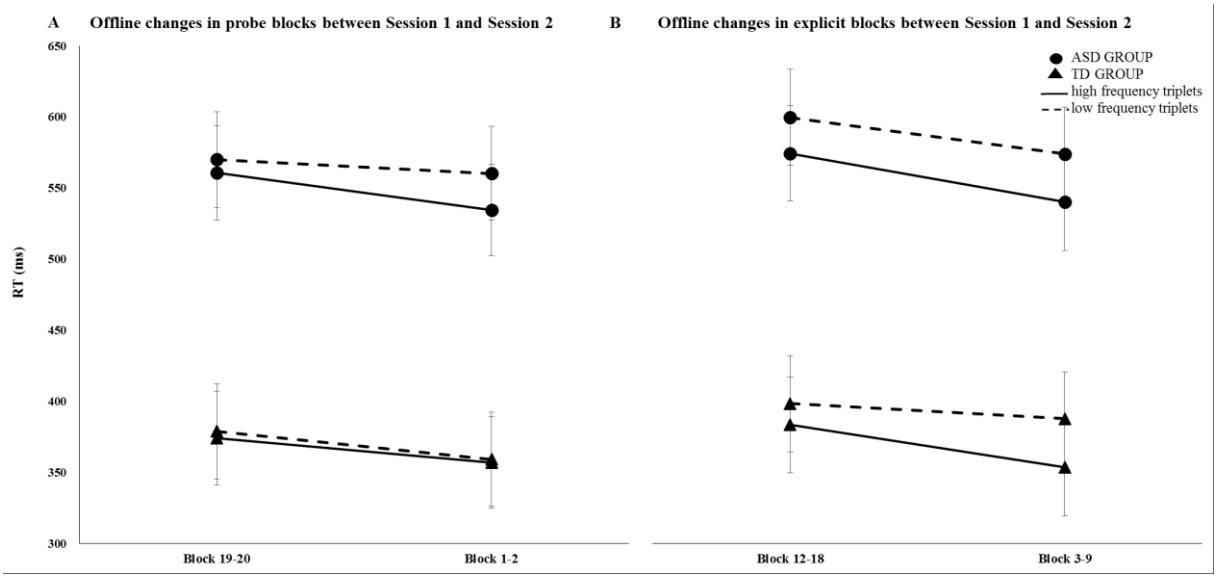

Figure 19. Offline changes in sequence-specific learning in ASD and TD groups in probe (A) and explicit (B) blocks. The gap between the solid (high frequency triplets) and the dashed lines (low frequency triplets) indicates sequence-specific learning. None of the two groups showed a significant difference in performance of probe and explicit blocks between Session 1 and Session 2, indicating that the participants managed to retain the sequence-specific knowledge they gained in Session 1. Error bars indicate standard error of the means.

Comparison of the first and second halves of the blocks in ASD and TD groups

We found significant group differences in within-block position effects, irrespective of sequence-specific learning: TD children showed on average slower RTs in the second halves of the blocks compared to the first halves, while ASD children showed similar RTs in the first and second halves indicated by the GROUP*HALFBLOCK interaction in the implicit probe blocks (F(1, 27) = 5.312, p = 0.029). These slower RTs in the TD children can indicate fatigue effects (Torok et al., 2017). The GROUP*HALFBLOCK interaction in the explicit blocks however was not significant (F(1, 27) = 0.030, p = 0.864), see in Figure 20.

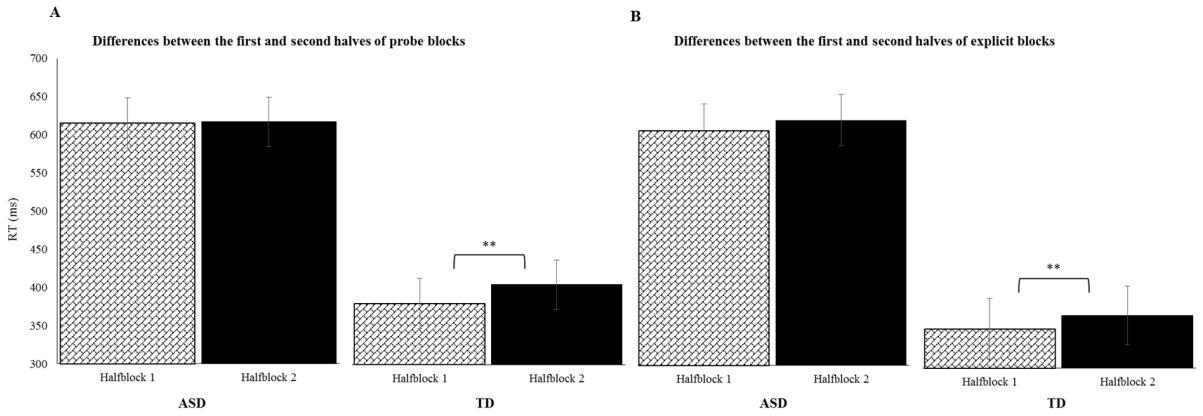

Figure 20. Differences in performance between the first and second halves of blocks. A indicates the within block effect on probe blocks, B indicates the within block effect on explicit blocks. A significant difference in performance between the first and second parts of the blocks was found in the TD group, however, this was not true for the ASD group. Error bars represent standard error of means.

Group differences in overall reaction times

Both in the implicit probe and explicit blocks the ASD group was generally slower compared to the TD group indicated by the main effect of GROUP (in the probe blocks: $F(1, 27) = 21.570$, $p < 0.001$; in the explicit blocks: $F(1, 27) = 19.618$, $p < 0.001$). To test whether this general RT difference affected the results of sequence-specific learning, we also conducted all our analyses with normalized data, and found the same pattern of results as reported above.

Discussion

The main goal of this doctoral work was to explore the relationship between implicit and explicit learning and memory processes. One of our objectives was to understand the specific brain areas involved in these processes, a further one was how they can possibly overlap. We were also interested in the complex patterns of cognitive decline that can possibly come with the impairment of such overlapping areas in different patient populations. Overall, we approached these questions by testing implicit versus explicit cognitive processes, including learning and memory, as well as consolidation capabilities of multiple patient groups with different psychiatric or neurological conditions.

Study I. Comparing frontal lobe functions and implicit sequence learning in AUD patients and healthy controls

In this study, we investigated how long-term alcohol usage impacts 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 intake impacts implicit processes (Duka et al. 2001; Kirchner and 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 significantly by alcohol consumption. To go more into detail, Kirchner and Sayette (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 clearer impact on explicit/more executive like processes, while its effects on implicit processes are either not present or still unknown (Duka et al. 2001). The above-mentioned literature is also in line with researchers proving that implicit learning processes are spared in Korsakoff syndrome (Fama et al. 2006; Oudman et al. 2011), which is a chronic disorder often caused by long-term alcohol dependency, affecting mainly the frontal cortical areas and the hippocampus. Further interpretations involve that alcohol leaves not only 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 more 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 (Ashby et al. 1998; Poldrack et al. 2001; Filoteo et al. 2010; Henke 2010). In line with our results, studies showed that weakening the interconnectivity between frontal lobe and other brain structures, in addition to the disruption of the frontal lobe engagement, can improve sequence learning (Filoteo et al. 2010). For example, a recent finding of Nemeth et al. (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 et al. 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 (Kaiser et al. 1997; Egner et al. 2005; Gruzelier 2006). 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 and 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 et al. 2000), and furthermore, it is possible that the striatum plays a role in WM/executive functions by modulating the inhibition of the PFC (Ashby et al. 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. 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 the 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. Despite 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, showing a competitive relationship among them.

Study II. Implicit sequence learning and consolidation in TLE

In this study, our aim was to get a better insight into how MTL regions participate in implicit learning processes. In order to specify the role of the MTL, we decided to compare implicit sequence learning performance of TLE patients and matched healthy controls, as we hypothesized that due to the course of epilepsy, TLE patients have impaired MTL regions.

Overall, we found that both TLE patients and healthy controls showed a general speed-up in responding, also, both groups managed to acquire sequence specific knowledge in the implicit learning task, however the two groups differed in terms of implicit learning performance. This result is in line with previous studies showing that an impairment of the MTL

results in an impairment in implicit learning performance, in a stem completion task (Baddeley et al., 1994), and in an SRT task setting with amnesic patients (Curran et al., 1997). Importantly, the latter study only found an impairment in the presence of higher order associations. Others showed relatively intact implicit learning performance compared to the impairment of explicit memory (del Vecchio et al., 2004), as well as intact performance on an SRT task setting (Nissen et al., 1987). However, the origin of this impairment is debatable, as in our experimental groups this difference was most visible when the first and the second session's performance was merged together. Overall, although TLE patients showed weaker implicit sequence learning performance compared to the controls, they still showed significant sequence learning, implying that the MTL impairment seen in the patient population does not entirely eliminate their sequence learning capabilities. Note that only a few patients from the TLE group were bitemporal patients, thus most patients had at least one relatively intact MTL, possibly taking part in the initial phases of learning. Also, within-block position effects can also be responsible to the slight difference seen between TLE patients and matched controls.

More fine-grained analyses such as examining within-block position effects have been in the focus of more recent implicit sequence learning studies because of the possible divergencies of brain involvement even within a learning block, due to different mechanisms (Nemeth et al., Török et a., 2017). During the first halves of learning blocks, it is hypothesized that one has to dredge the previously learned implicit rule of the task again, thus this process is more MTL dependent, while the second halves of the blocks are hypothesized to be more automatic, thus rely more on the fronto-striato-cerebellar network of the brain (Nemeth et al., 2013; Gamble et al., 2014). In our experimental dataset we found significant within-block differences between the first and the second halves of the learning blocks in the two groups. Also, the two groups varied in the amount of within-block differences, suggesting that the impairment of the MTL changes the pattern of within-block effects. Interestingly, within-block differences were greater in the performance of control participants, which requires further explanation. One possible explanation for this result is that due to the impairment of the MTL, during the first halves of the blocks, sequence specific knowledge cannot evolve as it does for healthy controls. Also, during the second halves of the blocks, which are less dependent on the MTL, we can see a further decrease in sequence specific knowledge. These results are in line with the previously mentioned study by Nemeth and colleagues (2013), which showed that MCI patients show smaller sequence-specific learning performance compared to controls in the first halves of the blocks , however TLE patients did not show an increase in the second halves of

the blocks either. These results suggest, that sequence specific knowledge is not able to sink in enough for the TLE patients so that due to a possible fatigue effect, sequence specific performance slightly drops by the end of the blocks.

Interestingly, we found no significant differences in the rate of consolidation of the learned material between the two groups, indicating that neither the TLE group, nor healthy controls showed significant forgetting of the learned material. Also, when looking at consolidation of the first and second halves of the experimental blocks, we found no differences in consolidation gain or the rate of forgetting between the two groups. Overall, we found no differences in consolidation patterns between the TLE group and the matched healthy controls. Supposing that the hippocampus might have a role in implicit memory consolidation (Nadel and Moscovitch et al., 1997; Albouy et al., 2008, 2013), we suggested that impairment of the MTL in TLE could result in some impairment in the consolidation of implicit sequence learning in the ASRT task. Overall, we did not find significant differences in consolidation patterns between the two groups, indicating that epileptic activity and impairment of the MTL does not change the consolidation pattern of implicit sequence learning, probably implying that the MTL is not involved in the consolidation of implicit sequence learning. Implicit learning experiments that rely more on contextual information (Chung and Phelps et al., 1999), found alterations in consolidation of TLE and amnesic patients, however the implicitness of the task does not mean by itself that solving it relies on the fronto-striatal network. This further implies that the MTL is involved in the consolidation of contextual information, probably irrespective of awareness during learning (Nadel and Moscovitch et al., 1997).

To sum up, we found that both healthy controls and TLE patients showed a general speed-up in responding, also, both groups managed to acquire sequence specific knowledge in the implicit learning task, however this knowledge was slightly impaired for the TLE patients, which we conclude as an impairment affecting higher-order associations mostly. Also, we did not find any differences in consolidation of the task between the two groups, which is in line with studies showing a more pronounced effect of sleep in more spatially dependent implicit memory tasks (Chun and Phelps et al., 1999; Nadel and Moscovitch et al., 1997), and probably reflects that the MTL is only involved in the earlier phases of implicit sequence learning. Interestingly, the two experimental groups varied in within-block performance as well, with the TLE group showing greater within-block performance differences. We explain these results as evidence that during the first halves of the blocks, sequence specific knowledge does not solidify for TLE patients as much as for healthy controls. Still, in the second halves of the

blocks we see a more pronounced RT decrease, indicating better performance on the less "MTL dependent" half of the blocks, suggesting that the slight impairment in the first halves of the blocks is due to MTL impairment in TLE.

Study III. Explicit learning and sleep related consolidation in TLE

Our aim was to get a better insight of sleep spindles and their role in learning and memory consolidation of TLE patients. We used two distinct analyses to approach this question, looking at both trait and state-like effects of sleep spindles on learning and memory consolidation, as well as other possibly interfering factors, such as the macrostructure of sleep, IQ and the years spent with epilepsy.

Our results are in line with previous literature showing an individual trait-like occurrence of sleep spindles in general (Schabus et al., 2009), suggesting that regardless of the daily cognitive load, sleep spindles have a general, fingerprint-like (Ujma et al., 2014) effect on one's cognitive abilities. Interestingly, this has already been evidenced in the healthy population, but this is the first study analysing multiple learning events and consecutive sleep of TLE patients. In TLE, several brain networks - including sleep spindle generator areas as well - are impaired. Therefore, according to our results, trait like sleep spindle features appear to be very similar to that of the healthy population's, however the frequency range of sleep spindles in relation to learning is generally slower for the TLE population, which could be accounted to the damage of faster sleep-spindle generating areas, but this requires further explanation. Sleep spindles are altered by epileptic activity (Staresina et a., 2015), furthermore, epileptic activity effects the symmetry (Clemens et al., 2000), as well as the number (Tezer et al., 2014; Frauscher et al., 2015; Lambert et al., 2017) of sleep spindles.

We did not find any significant state-like correlations between sleep spindles indexes and memory consolidation, which is surprising, as there are a great number of studies showing some kind of learning and consolidation dependent change in sleep spindle parameters, or vice-versa, sleep spindle dependent memory consolidation changes (Born et al., 2007; Rasch et al., 2007; Nishida and Walker et al., 2007, Morin et al., 2008). Our approach tried to address this question by normalizing both learning performance and sleep spindle measures to individual averages, to see whether there is a linear association between certain sleep spindle indexes and memory consolidation. Despite all the previous results on state-like sleep spindle and memory consolidation correlations (Gais et al.., 2002; Clemens et al., 2005), some studies have also

shown the absence of such state-dependent changes as well (Schabus et al., 2009). The absolute number of sleep spindles has been associated with both verbal and visuospatial memory retention (Clemens et al., 2005; Clemens et al., 2006). Previous experiments using a visuospatial learning paradigm (Clemens et al., 2006), found significant correlations with the number of sleep spindles over parietal regions and 24-hour retention of the engrams. We also found a positive relationship between the absolute number of sleep spindles and memory consolidation gain, however significant correlations localize to the right side, which is contralateral compared to what has been previously expected.

Our experimental paradigm was based on a verbal learning paradigm, which suggests that we should have seen positive correlations between sleep spindles on the dominant (mostly left) temporal and frontal electrode sites. However, this was not true in our case, as we mostly contralateral significant correlations between slow sleep spindle density, duration and the number of words recalled at certain learning rounds, as well as between consolidation and fast sleep spindle density and slow sleep spindle amplitude. One possible explanation for this is that epileptic activity induces reorganization processes. Such explanations can be supported by the growing evidence on the importance of reorganization processes of patients with TLE (Powell et al., 2007; Del Felice et al., 2017). However, Powell and colleagues (Powell et al., 2007) found that sustained activity of the affected hemisphere correlates with memory performance, while reorganization of a memory function to the contralateral hemisphere is not an efficient way of cognitive reserve. Still, a handful of studies found significant reorganization between left and right MTL in visuospatial memory (Figueiredo et al., 2008), as well as in verbal memory (Seidenberg et al., 1997; Wood et al., 1999; Thivard et al., 2005).

Fast sleep spindles are thought to be closely related to learning and memory consolidation (Tamaki et al., 2008), while slower sleep spindles are usually noted as a physiological result of thalamo-cortical activation, differing in the generator area as well (De Gennaro and Ferrara et al., 2003; Mölle et al., 2011). Our results indicate that for the TLE population, learning is mostly related to slower sleep spindles, while consolidation has a relationship with both slower and faster sleep spindles. These results may indicate that fast sleep spindles might be more affected by the pathological processes of TLE, resulting a possible shift towards slower sleep spindle frequencies in relation to learning, while consolidation processes are related to both slower and faster sleep spindles.

Our experimental paradigm has its limits, as it is almost impossible to rule out all possible confounding factors with patients participating in this experiment. Even though

learning took place in the evening, and participants were instructed not to do anything significant after the experiment, we cannot rule out that other activities during the day can also alter sleep spindle measurements, as well as general learning capacity. As the experiments were embedded in a period that participants spent at the EMU for seizure localization, we cannot completely rule out the effects of changes in one's antiepileptic drug administration, and the effects of ictal and interictal activity during the day.

Study IV. Implicit sequence learning and consolidation in ASD and the role of explicit instructions

Our aim was to gain better understanding of how performance of children with ASD varies within a task setting consisting of both implicit and explicit conditions. We used an experimental setup involving alternating uncued (implicit) and cued (explicit) probabilistic sequence learning task segments. According to our results, ASD and TD children did not differ in their performance on the explicit blocks, however when instructions were implicit, ASD children outperformed TD children. Following the 16-hour delay period both groups showed intact retention of the previously acquired knowledge. Also, we found an effect of fatigue in the second halves of blocks, but interestingly only for the TD group.

The superior performance of ASD children compared to TD children on probe blocks is in line with previous literature showing intact or even better performance of ASD children on various forms of implicit SRT tasks (Foti et al., 2015; Nemeth et al., 2010; Brown et al., 2010). Also, others found intact, however prolonged learning (Barnes et al., 2008) which is considered to be reflecting cognitive inflexibility.

Interestingly, the pattern of results in explicit blocks showed a distinct picture. In explicit blocks both ASD and TD groups performed similarly, however ASD group outperformed TD groups in implicit probe blocks. This is in line with the results of Travers and colleagues (Travers et al., 2010, 2015) found similar performance between ASD and TD children on an explicit SRT task, but came to the conclusion that despite showing similarities in overall performance, the learning strategy differs for the two groups, which in their case was further confirmed by differences in fMRI activation patterns as well. Regarding the retention of the acquired knowledge, we can conclude that the 16-hour delay period did not abolish the sequence learning gain from the first session, regardless of task conditions. Our results are in line with previous experiments measuring procedural learning of ASD children in a similar

setup, also showing significant retention of the acquired knowledge even after a period of delay (Nemeth et al., 2010).

According to our results, the transitional effects between probe and explicit blocks differ between the two groups suggesting that the ASD group is less sensitive to these shifts. One possible explanation is that the already developed learning strategy in ASD children does not change even when the implicitness/explicitness of the task changes. This unfolds the question why the transition between explicit and implicit blocks does not affect the performance of ASD children. In other words, ASD children can transfer the acquired probabilistic sequence knowledge from explicit blocks to the following implicit probe blocks and vica versa. This implies that ASD children do not switch the learning strategy, even if instructions or the structure of the task would require to do so. Such tendencies are in line with the decrease of cortical connectivity (Travers et al., 2015), the increase in subcortical connectivity (Hollander et al., 2005; Muller et al., 2004) and the deficits in flexible updating mediated by the orbito-frontal cortex (Solomon et al., 2011), all together leading to a more rigid learning strategy Gordon et al., 2007). Generally, rigidity in task switching situations can be a disadvantage, however according to our current results in probabilistic learning, it can also serve as an advantage.

Differences in the learning strategies of ASD and TD children can be further explained by structural and functional differences in their central nervous system. As already mentioned, some studies found decreased cerebellar and cortical connectivity for ASD children during a motor learning task (Mostofsky et al., 2009), while again others have shown that subcortical areas are not only intact but in some cases are increased in size and connectivity for ASD children (Hollander et al., 2005; Muller et al., 2004) and show functional differences as well. Roser and colleagues (2015) found that visual exposure to stimuli results in enhanced visual learning of statistical regularities for adults with ASD compared to healthy controls in a visual learning experiment. Superior performance of the ASD group in this task indicates that there is a pronounced visuospatial enhancement in ASD in the visual statistical learning domain. Additionally, procedural learning cued with contextual information is also intact or even improved in children with ASD compared to TD controls (Kourkoulou et al., 2012). Statistical learning of language regularities (Mayo et al., 2012) points to a similar direction, as high functioning ASD children and matched TD controls demonstrated similarly intact implicit learning of statistical regularities within an artificial language learning paradigm. Motor learning also shows a similar pattern, as ASD children and TD children show similar

performance in a motor procedural learning task (Sparaci et al., 2015), however from certain indexes of the task one can see that the strategy ASD and TD children use for such a task do differ. Overall, procedural learning seems to be intact for the high functioning ASD population, however the way learning occurs differs between TD children and adults. This difference might come from the orderliness of brain areas involved in learning for the high functioning ASD population (Schipul et al., 2011) and their lower structural and functional cortical connectivity (Just et al., 2007).

Finally, we found a within-block position effect for the TD children that was not related to sequence-specific learning (in contrast to the studies of Nemeth et al. (2013) and Gamble et al. (2014)). Instead, TD children showed generally slower responses in the second halves of the blocks compared to the first halves, while the ASD children did not show this pattern. This phenomenon might be due to a general fatigue effect, meaning that it is not learning-dependent (Torok et al., 2017). ASD children might be able to focus their attention more selectively on such types of tasks, excluding all other stimuli from their environment, and retain this highly focused attention throughout the task with relatively less effort compared to the TD children. On the other hand, it is also possible that children with ASD have a heightened skill for attenuating the instructions, thus they have an ability to only focus on the main patterns, rules and correlations of a task. Finding such an effect for TD children is in line with previous experiments finding slower responses in later trials in a given block in healthy adult participants (Torok et al., 2017; Rickard et al., 2008; Brawn et al., 2010).

To sum up, the present study found not only intact, but even superior implicit learning performance in children with ASD compared to TD children. Also, the two groups did not differ in their performance during explicit blocks, nor in overall consolidation effects. Furthermore, our results showed a resistance against fatigue effect in ASD. Our findings can help in planning more targeted therapeutic setups for ASD children or other populations showing a similar pattern of difficulties in learning.

General discussion

The focus of this doctoral work was on implicit and explicit learning and memory in three specific disorders, including ASD, AUD and TLE patient populations to have a more elaborated insight into how these learning and memory processes interact with other cognitive

functions and possibly interact with each other. These specific disorders were chosen to be the focus because all three represent a different set of cognitive impairments, therefore it can be very informative to see the overlapping and dissociating segments of implicit and explicit memory. First, we looked at how executive functions and implicit memory relate to one another, thus we explored the exact involvement of the frontal lobe in implicit skill learning. In the following, we looked at a possible involvement of the MTL in implicit skill learning and explicit learning, to see whether there is a dissociation between the two types of learning and memory in performance, as well as consolidation patterns. Finally, we took a closer look at whether shifts in the rate of awareness within an experimental setup have a significant effect on the performance of healthy individuals and ASD children, who are characterized by a decrease in cortical and cerebellar connectivity (Mostofsky et al., 2009), as well as an increase in subcortical connectivity (Hollander et al., 2005).

To our knowledge, our study was the first to investigate the effects of long-term alcohol usage on implicit sequence learning and how these indices correlate with performance on executive functions. Despite the common expectation that alcohol disrupts most cognitive functions, we showed that at least one function, specifically implicit sequence learning, is intact, however we found weaker executive functions at this patient group. Our results shed light on the different or partly overlapping fronto-striatal networks that have a different role in implicit processes and executive functions, showing a competitive relationship among them. Also, we found not only intact, but even superior implicit learning performance in children with ASD compared to TD children, suggesting that the frontal lobe differences between ASD and TD not necessarily impair the fronto-striato-cerebellar network, but instead result in a different mode of processing information. Also, the two groups did not differ in their performance during explicit blocks, nor in overall consolidation effects. Furthermore, our results showed a resistance against fatigue effect in ASD.

Next, we wanted to see how the MTL related to implicit sequence learning processes, also, to explore the role of sleep in implicit and explicit learning processes, to see whether there is a common consolidatory process between the two learning mechanisms. In the implicit sequence learning paradigm, we found that both healthy controls and TLE patients showed a general speed-up in responding, also, both groups managed to acquire sequence specific knowledge in the implicit learning task, however this knowledge was slightly impaired for the TLE patients, which we conclude as an impairment affecting higher-order associations mostly.

We explained within-block performance differences between the groups as evidence that during the first halves of the blocks, sequence specific knowledge does not solidify for TLE patients compared to the performance of healthy controls. Also, we did not find any differences in consolidation of the task between the two groups, which indicated that the ASRT task per se is not sleep dependent.

In the experiment measuring explicit learning of TLE patients, we found sleep related differences in relation to consolidation, indicating that there is a dissociation between explicit and implicit experimental setups in that consolidation of explicit knowledge is related to sleep, while consolidation of implicit sequence learning happens irrespective of sleep and is not impaired in the TLE group compared to healthy controls. Sleep related memory consolidation shows a similar pattern compared to previous results with healthy population, in that there is a trait-like relationship between certain sleep spindle parameters, learning and memory consolidation. However, a state-like relationship between explicit memory consolidation and sleep spindles was only found with the absolute number of sleep spindles overnight.

Overall, experimental paradigms of this work and the explored patient populations led us to a clearer knowledge on what the role of the frontal lobe is in implicit sequence learning paradigms and how impairments or differences in this area effect this type of knowledge. We also gained significant knowledge on how the MTL is related to implicit learning and memory, through examining implicit and explicit learning characteristics of TLE patients. Furthermore, we have a better understanding of the sleep related characteristics of explicit memory consolidation in TLE, as well as for the lack of sleep related differences in implicit sequence learning.

Future questions

ASD has been referred to as a continuity according to the rate of impairment in cognitive and social skill. For the purpose of this study, we chose to explore only the high functioning patients, but in the future, performance of less well functioning patients could reflect more visible changes in the fronto-striatal network, pointing out differences in vulnerability within this area, and its relation to implicit learning performance. Previous literature differentiated between automatically and conceptually driven aspects of implicit learning, which could be in relation to the intact implicit learning performance found in high functioning ASD and abstinent

AUD patients, implying that the areas which the more automatically driven tasks rely on are relative intact, however we don't really know how these conditions impact a more conceptually driven task, also, whether these two processes interact with one another or are independent.

Even though we found relatively intact implicit sequence learning in the TLE group, we still found within-block position differences, which, according to previous literature on how the initial phases of implicit learning is related to the MTL could reflect MTL related differences in learning. In order to explore the exact role of the MTL in implicit learning processes for TLE patients, we are planning to analyse the EEG data gained while performing the ASRT task. Also, to test the lack of sleep related differences in TLE patients and healthy controls in the implicit learning task, we would like to investigate whether there is a more specific relationship between implicit memory consolidation and sleep spindles or sleep macrostructure. Our experimental paradigms with TLE patients also have some limits. We cannot rule out that other activities during the day can also alter sleep spindle measurements, as well as general learning capacity, even though learning took place in the evening, and participants were instructed not to do anything significant after the experiment. As the experiments were embedded in a period that participants spent at the EMU for seizure localization, we cannot either completely rule out the effects of changes in one's antiepileptic drug administration, and the effects of ictal and interictal activity during the day.

Conclusion

The focus of this doctoral work was on implicit and explicit learning and memory in three specific disorders, namely ASD, AUD and TLE patient populations, to provide a more elaborated insight into how implicit and explicit learning and memory processes are related to one another. Overall, our experimental paradigms served us with a more detailed insight on the role of the frontal lobe is in implicit sequence learning paradigms and how impairments or functional differences in this area effect this type of knowledge. We showed that AUD patients show intact implicit learning capabilities, however we found that the intactness of executive functions modulates implicit learning performance, which indicates that the two functions are closely connected. Our results with the ASD population further nuanced these results, as we found not only intact, but even superior implicit learning performance in ASD children, and found no significant difference in the performance on the explicit task settings either. These results show that possible frontal lobe alterations of ASD children and different learning

strategies do not necessarily result in impaired implicit learning performance, instead, they seemingly exhibit intact or even enhanced implicit learning capabilities. We also gained significant knowledge on how the MTL is related to implicit learning and memory, through examining implicit and explicit learning characteristics of TLE patients. Here, we found that despite the impairment of the MTL, TLE patients were able to acquire and retain sequence knowledge implicitly, although their learning performance was weaker compared to the healthy controls, suggesting that the MTL might have at least some role in implicit learning. Additionally, alterations in within-block effects also emerged, warranting future research to gain further insights into the learning processes and their neural substrates in implicit sequence learning using more fine-grained analyses. Furthermore, we also gained better understanding of the sleep related characteristics of explicit memory consolidation in TLE, including similarities and dissimilarities of memory consolidation and its relation to sleep spindles in the TLE population compared to previous literature on healthy population. Future questions still remain unsolved in these topics, including implicit learning and memory in less well functioning ASD, as well as the electrophysiological characteristics of implicit learning and memory in comparison to explicit learning including online learning and consolidation as well.

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