Thesis booklet

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

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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). Plasticity is the basic feature of the central nervous system, thus there are special networks in the brain, developed to create optimal conditions for the emergence of more complex associations in learning and memory. Still, the vast majority of neuroscience focuses on the mechanism of learning and memory, gaining substantial understanding of the underlying cellular and network mechanisms.

Neurodegenerative diseases are one of 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 common 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. Neuropsychology has been greatly supported by the evolution and expansion of modern brain imaging techniques, and 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.

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. 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. 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.

Background

Recently, 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 (Schendan et al., 2003). Experiments with amnesic patients have shown that there is deficit in implicit learning of contextual information, further suggesting 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). Behavioral experimental data shows that in Mild Cognitive Impairment (MCI), there is an impairment in implicit learning, especially in the initial phases, also suggesting an MTL involvement In summary, the MTL possibly plays 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.

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. 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 development of these skills and their interaction with other cognitive processes/functions is crucial to understand how skill learning occurs. 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).

The frontal lobe, especially the PFC is involved in implicit learning processes, even if the underlying sequence is completely hidden for the participants (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., 1996; Peigneux et al., 2000). However, there is also evidence for a lack of direct relationship (Janacsek and

Nemeth et al., 2013) or an interference (Nemeth et al., 2013; Blackwell et al., 2014) between working memory and implicit learning performance, implying that there is a fine balance between frontal lobe mediated cognitive resources and cognitive resources for implicit learning, possibly mediated by general cognitive abilities (Pretz et al., 2010). 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 disfunction, 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. 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.

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. 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. Such memories can be retrieved in form of recognition as well as by free or cued recall (Tulving & Wiseman, 1975). Also, recognition and recollection differ in hippocampal involvement as well (Eichenbaum et al., 2004). 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 a validated test to measure this effect. 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, leading to a widespread literature. We also used a modified version of this task in one of our experimental setups.The original 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, followed by an interference word list (list B) and two delayed recalls.

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, such as neocortical structures are also important in mediating 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). Explicit memory consolidation relies greatly on the communication between hippocampal and neocortical areas during sleep. 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, which is related to the synchronizing characteristics of slow wave activity (SWA) during sleep (Walker et al., 2004; 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). 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.

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.

Our focus

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 is still unknown. 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 (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 ever investigated implicit sequence learning capabilities in TLE only (without any other neurological disorders present). Increasing evidence suggests that ASD children show intact implicit learning abilities on most experimental setups, however their performance differs in the strategy they use, as well as according to the extent of certain brain areas involved in these processes. 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.

Empirical studies and theses

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.

Study 1

T1: Executive functions show a competitive relationship with implicit learning processes.

T2: Implicit learning processes are intact in the alcohol usage disorder (AUD) group.

Study 2

T3: Implicit learning is impaired in temporal lobe epilepsy.

Study 3

T4: Temporal lobe epilepsy has a modulatory effect on learning and consolidation of explicit knowledge and its relation to sleep spindles.

Study 4

T5: Implicit sequence learning performance of children with Autism Spectrum Disorder (ASD) is intact or even superior compared typically developing children.

T6: Explicit shifts in an implicit sequence learning task alter performance of ASD children.

Methods and results

Study 1

According to the framework of competitive neurocognitive networks, disrupting specific frontal lobe functions, such as executive functions, increases performance on implicit learning tasks, thus we expected a similar association in this patient population as well. 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.

The alcohol-dependent (N=14) and the control groups (N=16) were matched in age, gender and years of education. History of participant's alcohol dependency was diverse, still, according to the number of relapses all participants have had at least one relapse. Controls participants demonstrated normal neurological behaviour and were not taking any psychoactive medications. The ASRT task was administered in one session. Participants were informed that the main aim of the study was to find out 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, without any explicit or implicit information about the regularity of the embedded sequence. 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. 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.

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. Overall, participants responded faster to high-frequency than low frequency triplets, revealing successful sequence-specific learning, also, participants showed general skill learning improvement as well. There was no difference between the alcohol-dependent and the control groups in sequence specific learning. In a following ANOVA, we also included EXECUTIVE GROUP (low vs. high) as a between-subjects factor. Here, executive functions had an effect on sequence-specific learning in the ASRT task, such that 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).

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 when the alcohol-dependent and the control groups were analysed together. Within-group correlations showed similarly moderate, negative correlation in the control group and a relatively strong negative correlation in the alcohol dependent group. 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. 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 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.

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.

T1: 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.

T2: We found intact implicit learning in the AUD group. Despite the common expectation that alcohol disrupts most cognitive functions, we showed that implicit sequence learning, is intact.

Study 2

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 and the possible effects a decline in the functioning 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, mostly relating to contextual and relational information. Here we hypothesized that if the MTL has a role in implicit learning processes, then we should find an impairment in the performance of the TLE population in a skill learning task compared to healthy controls. TLE patients (N=12), and age and gender matched healthy controls (N=12) 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. 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, blocks were organized into 4 implicit blocks in each session. We decided to make the task shorter for the TLE patients, because we assumed that over 5 blocks, the effect of fatigue would diminish sequence specific learning. This way, the task lasted for about 20-25 minutes at each session.

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, and we found significant differences in sequence-specific learning between the TLE group and matched healthy controls. The control group showed greater sequence specific learning compared to the TLE patients. Participants showed general speed-up during the task, irrespectively of triplet types or group. We looked at performance in the 8 epochs together to see possible within-block differences in performance. 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. Analysis of consolidation effects between Session 1 and Session 2 showed that participants did not show forgetting of the sequence. Participants showed an offline general speed-up in performance, irrespective of the group, which was also true for sequence-specific learning. The ANOVA suggested that participants did not show forgetting of the sequence, irrespective of within-block position. Also, offline changes in average RTs (general speed-up) were similar in the first and second halves of the blocks, which was also true for sequence-specific learning, irrespective of groups.

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 slighter 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.

T3: Overall, we found differences between healthy controls and MTL impaired TLE patients, thus we can conclude that we found that the MTL has a role in implicit skill learning processes.

Study 3

The third study also included TLE patients, 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. TLE patients (N=20) were included in the present study. Experiments were performed in the Epilepsy Monitoring Unit (EMU) of the National Institute of Clinical Neurosciences in Budapest. EEG was conducted by a standard 10-20 positioned 32 channel recording. 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. 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). 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). 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. 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.

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. 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. Overall, the number of words recalled per learning rounds showed a negative relationship with the years spent with epilepsy syndrome. To the contrary, years spent in education correlated positively with performance on almost all learning rounds. 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.

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. 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, and slow spindle duration on various electrode sites (F8, T4), indicating a trait-like relationship between slow spindle density, duration and learning performance in the TLE population. 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.

Average overnight consolidation showed a positive correlation with average slow spindle amplitude at electrode sites at the right hemisphere, however 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. 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.

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. 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, but we didn't find any significant correlations between macrostructural parameters and learning or consolidation scores.

T4: Our results indicate that TLE has a modulatory effect on learning and consolidation of explicit knowledge and its relation to sleep spindles. We found strong associations between general learning skills and general slow sleep spindling, and between spectral power in the faster sleep spindle frequency range and explicit memory consolidation. The laterality if these associations suggest that over the course of TLE, there is reorganization in these associations as well.

Study 4

Our fourth experimental population included children with ASD and matched healthy controls, to have 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 enabled 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.

Children with Autism Spectrum Disorder (N=14) (ASD) and age and IQ-matched typically developing (N=14) (TD) controls participated in the experiment (Table 6). We used a modified version of the ASRT task to measure implicit skill learning (probe blocks) and the possible effects of explicit

instructions on implicit learning performance (explicit blocks). An evening learning phase (Session 1) was followed by a testing phase in the morning (Session 2), separated by a 16-hour interval period.

We found differences in sequence-specific learning between the ASD and the control group in the probe blocks. While the ASD group exhibited significant learning, the control group did not learn the sequence. Participants showed general speed-up during the task, irrespectively of triplet types. We also found differences in general skill learning between the ASD and TD group, with more speed-up for the ASD group. Both ASD and TD groups managed to acquire sequence-specific learning in explicit blocks as well, however there was no difference in sequence-specific learning between ASD and TD groups in the explicit ASRT blocks of the first session. Participants showed general speed-up during the task, irrespectively of triplet types. Analysis of consolidation effects between Session 1 and Session 2 showed that participants did not show forgetting of the sequence. Also, there was no offline general speed-up, irrespective of triplet types and group, which was also true for sequence-specific learning. Overall, participants did not forget the sequence during the offline period in the explicit blocks either irrespective of the group. 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 in the probe blocks. These slower RTs in the TD children can indicate fatigue effects (Torok et al., 2017).

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.

T5: We found that implicit learning performance of ASD children is not only intact, but superior when compared to controls.

T6: We also found that explicit shifts in an implicit sequence learning task do not significantly alter performance of ASD children, however the gain in performance improvement between the ASD and healthy control group disappeared when explicit instructions were given.

Discussion

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, as well as an increase in subcortical connectivity.

First, we showed that implicit sequence learning is intact in the AUD group, 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.

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 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. 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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Az implicit szekvencia tanulás vizsgálata FO elektródával beültetett temporális lebeny epilepsziás betegeken. Virág M., Janacsek K., Dr. Fabó D., Dr. Németh D., Dr. Erőss L. A (2014, Magyar Idegsebészeti Társaság, és a Magyar Neuroonkológiai Társaság 2014. évi Nemzeti Kongresszusa, Budapest, poster)

Competition between frontal lobe functions and implicit sequence learning – evidence from the long-term effects of alcohol. Virág M., Janacsek K., Dr. Fabó D., Dr. Németh D. (2015, MITT, Budapest, poszter)

Implicit sequence learning in temporal lobe epilepsy patients with bilaterally implanted foramen ovale electrodes. Virág M., Dr. Erőss L., Dr. Fabó D. (2015, MITT, Budapest, poszter)

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