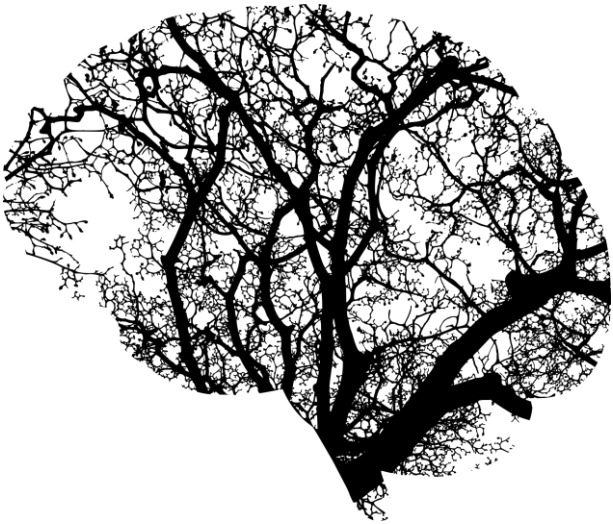
Visual learning: healthy development and the effects of migraine

PhD thesis



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Introduction

Learning refers to a change in behaviour that results from acquiring knowledge about the world. Based on the modality of the input (i.e. visual, auditory, somatosensory, etc.) learning can be further divided. Memory is the sum of processes by which knowledge is encoded, consolidated (stored), and later retrieved. These two functions give us the ability to adapt better to our environment, and are essential to the full functioning and independent survival of both humans and animals. Memory is traditionally divided into the sensory register, short-term memory and long-term memory. Viewed from the aspect of the consciousness of recollection, long-term memory can be divided into two systems: implicit and explicit memory.

Explicit (declarative) memory is the process that allows the conscious recollection of previously stored information. The system processes information from all sensory modalities. The explicit subsystem is known to be highly flexible: the information stored here is accessible to multiple response systems, so multiple pieces of information can be associated under different circumstances (so changing surface characteristics or modality of stimuli has little to no effect on this type of memory). The learning realized via this system is fast, but forgetting and retrieval failure may occur.

Explicit memory is centered around the medial temporal lobe (MTL), with key structures being the hippocampal formation (consisting of the hippocampus proper, dentate gyrus and subicular region) and adjacent cortices (parahippocampal cortex, entorhinal cortex, perirhinal cortex). Further structures associated with declarative memory include the prefrontal cortex, the inferior temporal cortex and the medial thalamus.

This system shows a slow development. The volume of the hippocampal formation increase sharply during the first 2 years of life, then continue to grow at a more moderate pace, reaching the peak volume in preadolescence (9-11 years). As for aging, the volume of

hippocampus is relatively preserved until 60 years of age, after which volume loss is observed. The prefrontal cortex, on the other hand, shows development well into the late adolescence, but starts to shrink from early adulthood by 5-10% per decade. Functionally a similar developmental trajectory can be observed: a marked increase in performance during the first years of life, which continues in later years of childhood into adolescence, and a decline of performance already apparent by the age of 50, a tendency which grows stronger as age advances

Implicit (nondeclarative) memory does not rely on conscious recollection, it is rather expressed through performance. Nondeclarative memory differs from the declarative system in a number of characteristics. First, in contrast to explicit memory, learning occurs gradually, at a relatively slow pace (with the single exception of priming). Second, it is much more durable and reliable. Third, it is inflexible, the information is not readily expressed by response systems that were not involved in the original learning (thus, it is sensitive to modifications of conditions: changes in modality, surface characteristics, or other alterations).

This system is anatomically diffuse and covers a diverse range of functions, such as procedural learning (associated with the basal ganglia, especially the neostriatum, however the hippocampus is also suggested to contribute to this function), associative learning (thought to be the function of the cerebellum, amygdala, and the basal ganglia play an important role in the reward-driven mechanisms of this function, with the dopaminergic substantia nigra-striatum connection, alongside with the ventral tegmental area - hippocampus pathway) and priming (a neocortical function).

Elements of the implicit system mature earlier than those of the explicit one. The caudate nucleus is thought to be quite mature already at birth, but shown to grow rapidly in the first two years, reaching peak volume at the age of 10-14 years. During the later lifespan, starting from early adulthood, a linear decrease in striatal volume (up

to 10% per decade) was reported. This system matures earlier functionally as well, with some types of learning being already present in the first months of life. On the other hand implicit functions are well preserved until an older age: decrease in performance only starts to appear around 70 years of age

Acquired Equivalence (AE) is a learning paradigm, which tests both implicit and explicit learning. In this form of learning subjects learn to that two or more stimuli (referred to as antecedents) are mapped onto the same outcomes or responses (referred to as consequents), thus they are equivalent in this sense. The Rutgers Acquired Equivalence Test (RAET) was used in numerous studies to test human AE performance. In the training phase (or association phase) of RAET the subjects learn in a step-by-step manner the associations of antecedents and consequents. Unbeknownst to the subjects, the associations follow a rule. In the testing phase they had to apply this rule (i.e. transfer, generalize).

Performance in the RAET paradigm has been examined in various neurological conditions. Patients with Parkinson's disease were found to underperform mainly in the association phase, while patients with hippocampal atrophy and Alzheimer's had problems mainly in generalization phase. Based on these, the association phase is thought to be mediated mainly by the basal ganglia, while generalization is thought to be a hippocampal function.

As for the changes of RAET task performance in aging, young adults were found to outperform older adults in both the association and generalization phases, with a marked decrease in generalization performance above 70 years. On the other hand, no information is available on the early development of this function.

Migraine without aura (referred to as migraine from this point forward) is a common chronic neurological condition, one of the primary headaches. According to the ICHD-3beta migraine is distinguished by recurring episodes of headache that come in attacks

lasting 4-72 hours, characterized by at least two of the following: unilateral location, pulsating quality, moderate or severe pain intensity and aggravation by or causing avoidance of routine physical activity; and at least one of the following associated symptom during headache attacks: nausea and/or vomiting, photophobia and phonophobia.

Neuroimaging studies found several alterations in the brain of migraineurs. A decrease in grey-matter density could be observed primarily in somatosensory discriminative regions: the primary and secondary somatosensory cortices, dorsolateral part of the prefrontal cortex and orbitofrontal cortex. A significant increase of hippocampal and caudate grey matter volumes was discovered in low-frequency migraineurs, however, with the rise of the attack numbers, the volumes of these areas appear to decrease. Deep white-matter lesions have also been described, and the possibility of atrophy and axon loss was raised as well. An increased prevalence of stroke was also found in migraine patients. The majority of these lesions were subclinical, and were present in the posterior circulation territory, localised mainly infratentorially, typically in watershed-zones of the cerebellum. fMRI studies found a decrease in the intraregional functional connectivity density of several brain regions (e.g. prefrontal cortex, anterior cingulate cortex, insula, the hippocampus and nuclei of the basal ganglia system).

Aims of the study

The aims of the study were to examine the healthy development of learning functions associated with the hippocampus and the basal ganglia using a simple, noninvasive psychophysical test (the modified Rutgers Acquired Equivalence Test, translated to Hungarian), to provide data on the age- and sex related functional development of the associated structures (Study #1). We also intended to investigate if migraine causes any changes of performance in these learning functions (Study #2).

Materials and methods

Participants: All subjects were of Caucasian race and of similar socioeconomic status (middle class). Only patients with negative history of ophtalmological, neurological (the migraine of the migraine patients in study #2 was an exception) and psychiatric conditions were eligible for the study. Both study protocols conformed to the tenets of the Declaration of Helsinki in all respects, and it was approved by the Regional Research Ethics Committee for Medical Research at the University of Szeged, Hungary (approval number: 52/2015).

- **Study #1**: 265 healthy subjects (n_{female}=149, n_{male}=116, age range: 3-52 years) were recruited on a voluntary basis. Children were recruited from a kindergarten, an elementary school and two high schools. Adult subjects were volunteers from among co-workers of various departments of the University of Szeged.
- **Study #2**: 22 migraine patients were assessed (2 males, 20 females, age range: 20-52 years, median: 42.5 years). Subjects were recruited from among patients of the Neurology and Stroke Department of the Hospital of Kecskemét, Hungary. The inclusion criterion was a diagnosis of migraine without aura, set up by the same neurologist according to the ICHD-3beta. In all cases, at least five days had passed since the last attack at the time of testing, and no attack occurred in the 24 hours following the testing. The control group consisted of 22 healthy volunteers matched to the migraineur group in sex, age and level of education. The exclusion criteria were the same as in the migraineur group, with the extra requirement that the participant had no history of any kind of headaches. Controls were recruited from among the co-workers of various departments of the Faculty of Medicine.

Materials were the same in both studies. The tests were run on a Lenovo ThinkPad T430 laptop computer and two iBook G3 "Clamshell" laptop computers. Two adjacent buttons located approximately in the middle of the keyboard (letters “G” and “H”) were labelled visibly as “LEFT” and “RIGHT” respectively. The

testing software was written in Assembly for Windows. The software was a modified and translated form of RAET (original version by Myers and colleagues at Rutgers University, NJ (Myers et al. 2003), written for iOS), used and modified with the written permission of the corresponding author. The testing sessions took place in a quiet room with the subjects sitting at a comfortable distance from the computer screen. One subject was tested at a time, and no time limit was set so that the subjects could concentrate on the task.

Procedure: The testing protocol used was identical in the two experiments. The testing was done according to Myers et al. (2003), modified as noted above. The task was a two-alternative forced choice task, on each trial of which, participants saw a cartoon face and a pair of cartoon fish, and had to learn through trial and error which of the fish went with which face. There were four cartoon faces (male adult, a male child, a female adult and a female child) and four possible fish of different colours (red, green, blue and yellow), referred to in the terminology of Myers and colleagues (2003) as antecedents and consequents, respectively. The antecedent-consequent pairings were randomly generated by the computer from these stimuli for each participant. The paradigm consisted of an association (or acquisition) phase (visual feedback on the correctness of choice was provided), and a test phase (or transfer) phase (no feedback was provided). Association phase was further divided into three sub-phases. During the first (shaping) the participants learned the pairings of two antecedents and consequents (e.g. the male adult is paired with the yellow fish, the male child is associated with the green fish). In the second sub-phase (equivalence training) two more antecedents were mapped to the two consequents used in shaping (e.g. the female child – just as the male adult – is associated with the yellow fish, the female adult – as the male child – is associated with the green fish). Thus two-two antecedents (e.g. male adult-female child, male child- female adult) were trained to be equal in this aspect. In the third sub-phase (new consequents) two antecedents were associated to new, hitherto unseen consequents (e.g. the male child is paired with the red fish, the female child is paired with the blue fish). New associations were

introduced one by one during the association phase. New associations were presented mixed with trials of previously learned associations. The subjects had to achieve a certain number of consecutive correct answers after the presentation of each new association to be allowed to proceed, thus association phase trial number depended on performance. Test phase consisted of retrieval (36 trials, known associations), and generalization (12 trials, two pairings that were not shown during the association phase but could be deduced based on the equivalence rule).

Statistical analysis of the results were done in four groups: the number of trials necessary for the completion of the association phase (number of acquisition trials, NAT), and the ratio of correct and wrong answers during association phase (association learning error ratio, ALER), retrieval (retrieval error ratio (RER) and generalization (generalization error ratio, GER). Statistical analysis was performed in SPSS 21.0 (IBM, USA) except for the power calculations, which were done in G*Power 3.1.9.2. (Universität Düsseldorf, Germany).

- **Study #1**: For further analysis participants were distributed in 14 cohorts based on age: kindergarten children (3 to 6 years of age), 8 grades of elementary school children (7 to 14 years of age), high school students (15-19 years), and adults aged 20 to 29, 30 to 39, 40 to 49, and 50+. The results were analysed with factorial analysis of variance (ANOVA). Sex and cohort were selected as predictors.
- **Study #2**: As the Shapiro-Wilk test indicated normal distribution for all studied variables, one-way ANOVA was used for the comparisons. Additional linear regression analyses were performed to determine if any of the examined migraine characteristics (e.g. migraine history in years, attack frequency per month, estimated total attack number) had effect on the target variables in the migraine group.

Results

Study #1: The development of AE

The achieved power for the factorial ANOVA was 0.88 (f=0.25, α=0.004, sample size=265, number of groups=14).

The number of acquisition trials (NAT): according to the factorial ANOVA analysis sex had no significant effect ($F(1.265)=3.433$, $p=0.07$, two-tailed), however, cohort did ($F(13.256)=2.505$, $p<0.001$, two-tailed). Their interaction was not significant ($F(13.254)=0.701$, $p=0.76$, two-tailed). The Tukey's post-hoc analysis revealed that kindergarten children needed significantly more trials to acquire the associations than members of any of the other cohorts ($p=0.05$-0.001).

Association learning error ratio (ALER): sex did not have a significant effect on this parameter ($F(1.265)=3.690$, $p=0.06$, two-tailed), but cohort did ($F(13.256)=2.505$, $p<0.001$, two-tailed). Their interaction was not significant ($F(13.254)=1.253$, $p=0.24$, two-tailed). The post-hoc analysis revealed that kindergarten children made significantly more mistakes during acquisition than members of any of the other cohorts ($p<0.001$), and no significant differences were found among the rest of the cohorts.

Retrieval error ratio (RER): Sex did not have a significant effect ($F(1.265)=2.950$, $p=0.09$, two-tailed), but cohort did ($F(13.256)=4.757$, $p<0.001$, two-tailed). Their interaction was not significant ($F(13.254)=1.157$, $p=0.31$, two-tailed). The post-hoc analysis revealed that kindergarten children made significantly more mistakes during retrieval than members of any of the other cohorts ($p<0.001$), and no significant differences were found among the rest of the cohorts.

Generalisation error ratio (GER): Factorial ANOVA indicated no significant effect of either sex ($F(1.265)=0.099$, $p=0.75$, two-tailed) or cohort ($F(13.265)=0.934$, $p=0.52$, two-tailed). Neither was their interaction significant ($F(13.265)=0.601$, $p=0.85$, two-tailed). The success of generalisation was fairly constant in the studied period.

Additional analyses: To investigate whether the efficiency of

acquisition or the efficiency of retrieval had a significant effect on the success of generalisation, a multiple regression analysis was performed with GER as the dependent variable and NAT, ALER and RER as the independent variables. Neither NAT (β=-0.004, p=0.965) nor ALER (β=0.021, p=0.829) proved to be significant predictors of GER. On the other hand RER was a highly significant predictor of GER (β=0.503, p<0.001). ALER also had a significant effect on RER (β=0.673, p<0.001), suggesting that the less mistakes a subject made during acquisition, the more likely it was that they would successfully retrieve the stimulus pairs during testing - and the more efficient retrieval was, the more likely it became that the subject would generalise successfully.

Study #2: The effects of migraine on AE performance

Association learning error ratio (ALER): The mean error ratio during the association phase was significantly higher in the migraine group than in the control group (0.16 vs. 0.078, mean error ratios; migraineurs and controls, respectively; F=9.078, df=1, p=0.011, two-tailed; η^2=0.144).

Number of acquisition trials (NAT): The migraine group needed significantly more trials for the completion of the association phase than the controls ($n_{MIGRAINE}$=118.8 $n_{CONTROL}$=56.5, mean number of trials; F=6.691, df=1, p=0.016, two-tailed; η^2=0.130).

Retrieval error ratio (RER): In case of the known pairs during generalization phase, the two groups did not show significantly different error ratios (0.077 vs. 0.033, mean error ratios, migraineurs and controls, respectively; F=3.762 df=1 p=0.06, two-tailed; η^2=0.043).

Generalization error ratio (GER): The difference was highly different between migraineurs and controls, indicating the advantage of the control group (0.474 vs. 0.083, mean error ratios, migraineurs and controls, respectively; F=22.306, df=1, p<0.001, two-tailed; η^2=0.288).

Additional analyses: Nor interval therapy (flunarizine) nor any examined migraine characteristics (migraine duration in years, attack

frequency per months, estimated total number of attacks during the individual's lifetime had any effect on performance in any of the test stages ($p>0.05$ for all cases).

Discussion

The effect of age on AE performance

We found age related development in AE performance, specifically in pair acquisition and retrieval. In the examined age range, only one group differed significantly from all others: participants of kindergarten age (3-6 years) showed weaker performance. Over the age of 6, however, both the association phase and retrieval error ratios stabilized in a narrow, lower range. The developmental trajectory of generalization was somewhat similar, however, the leap between the performance of the two youngest cohorts was not significant. No significant change of performance was seen in the higher end of the examined age-spectrum. These findings are, in fact, rather surprising, considering the developmental course of the structures traditionally associated with the respective parts of RAET.

Myers and colleagues (2003) originally examined patients suffering from either Parkinson's disease or hippocampal atrophy. Based on their results they concluded that association is driven by the basal ganglia, while generalization is a hippocampal function. While the fMRI findings confirmed the latter, demonstrating that hippocampus indeed shows the highest activity among MTL structures during generalization task, the picture seems to be more complex. The association phase itself is mediated by both the explicit and the implicit systems, as it is partly an explicit reinforcement driven learning, partly an implicit category learning task. The explicit component is rather apparent, as the pairings can be described easily in a verbalized, declarative way. As it is a feedback driven associative learning, the basal ganglia probably contribute as well, through the striatum - substantia nigra (SN)/ventral tegmental area (VTA) - hippocampus connections. The activity of the striatum – VTA/SN

connection is higher during the early stages of learning, then, as learning progresses, the reward-related response in the caudate nucleus diminishes. On the other hand, the VTA – hippocampus connection shows a gradual elevation in activity related to successful learning. The category learning component also probably involves the basal ganglia (specifically the neostriatum) and the MTL. MTL has been described to govern responses in the early stages of category learning, then, over the course of training, the performance becomes increasingly dependent on the striatum. There is evidence to suggest that this reciprocal negative correlation might be mediated by the prefrontal cortex. On the other hand, as task complexity was found to correlate with activity of the striatum in various tasks, the simplicity of the category learning component in RAET predicts a lower activity in this network.

We hypothesize that the sum of these effects controls association acquisition during AE. The striatum has a role both in the explicit, reinforcement-driven learning, and in gaining implicit knowledge of the underlying rule. According to the fMRI data from earlier studies, the former procedure, associated with decreasing striatum activity is the dominant. VTA/SN activity increase, associated with reward-based learning was also observed. The hippocampus has a role in both the explicit and implicit component, as well as in compiling and applying the rule derived from the information collected by the basal ganglia. These are reflected in the gradual increase of hippocampal activity during the association phase, and the elevated activity during generalization.

Considering these, our results can be explained by a hypothesis proposing that the success of acquisition depends on the relationship of the two memory systems. More precisely, the effectiveness of the implicit component relies on how effectively the explicit activity is suppressed. This is consistent with the COVIS (COmpetition between Verbal and Implicit Systems) model that includes three systems: the explicit and implicit (that compete for access to response production) and one that monitors the output of these two systems and selects a

response to each trial. The model postulates that humans are biased toward the explicit system, and this initial bias must be overcome for a successful implicit learning to occur. We propose that the reason of the children's weaker performance is that the system component responsible for switching between explicit and implicit response is less developed than in later ages. A likely candidate for the component switching between memory systems is the prefrontal cortex, that is known to send extensive projections to both the hippocampi and basal ganglia, and was shown to be involved in their reciprocal activity. The prefrontal cortex matures long after the other two components, which may explain why we see an improvement of performance relatively late into childhood. In fact, as the development of this structure continues into late adolescence, in theory we should be able to see a weaker performance up to that point. For that reason, we hypothesize that a longer trajectory of improvement could be observed with a more sensitive test.

The lack of significant development in generalization might be explained by the fact, that the hippocampus shows the most marked structural maturation in the first two years of life Therefore, in the studied age range, the majority of hippocampal development is already over.

Another hypothesis to explain the high generalization performance of kindergarten children proposes that generalization depends on the hippocampus-VTA/SN-striatum rewarding network. There are two ways in which this system may be part of an explanation. First, the components of this network are thought to be mature at an earlier age than the lower limit of the range we examined. Second, the information is processed through both the striatum-SN and the VTA-hippocampus pathways, therefore the parallel activity of these connections might compensate if some of the underlying neural substrates are less developed.

Finally, the lower retrieval performance in kindergarten children is likely to be the result of the prefrontal cortex's less developed state as

well. While the retrieval of visual information depends most strongly on the inferior temporal cortex (an area that matures relatively early), the prefrontal cortex has been described to execute the higher control of this.

We did not observe age-related decline in performance. This is consistent with previous findings, describing that the decline becomes apparent only in a higher age range.

The effect of migraine on AE performance

Our results denote that migraine does significantly affect RAET performance. Migraineurs had greater difficulty in acquiring associations, reflected in both significantly higher NAT and ALER. The recall performance on the other hand was on par with that of controls. However, the results show that generalization was strongly impaired. Migraineurs had a significantly higher error ratio in case of pairings previously not encountered (they performed at chance level or worse), showing that they could not acquire and apply the underlying equivalence rule. In contrast controls had an error ratio below one percent.

In the light of the previously mentioned findings about migraine damaging both the striatum and the hippocampi, our results can be interpreted as behavioural evidence of those structural changes. Previous studies described an initial increase of caudate and hippocampus volumes in migraineurs, which is followed by a gradual decrease to a normal size as migraine progresses. However, our results demonstrate that this is probably not a return to the healthy state, rather a gradual atrophy of the altered structure, as the difference is obvious between the caudate-associated learning functions of migraineurs and controls.

A further explanation is that these functional changes are not a direct result of hippocampal and caudate dysfunctions, rather of some connecting structure. One possible structure is the prefrontal cortex,

which indeed was found to be affected in migraine. Another possibility is that the disruption of the dopaminergic striatum-SN/VTA-hippocampus network leads to the weaker AE performance in migraine patients. This latter is corroborated by findings of decreased RAET performance in other conditions involving disturbance of this system, namely Parkinson's disease, and long-term cocaine use. Patients suffering from these conditions are characterized by decreased acquisition performance. While no significant SN alteration was found in episodic migraine, VTA activation was found in the premonitory phase of nitroglycerine induced migraine attacks, therefore the involvement of these structures in the decreased learning functions in migraine is possible.

Conclusion

We conclude that acquisition shows significant age-related development, which can be explained with the longer developmental trajectories of different structures connecting to the basal ganglia and hippocampus (e.g. prefrontal cortex). On the other hand, generalization is adult-like quite early in childhood, regardless of sex. Furthermore, generalization can be highly efficient even when the learning of stimulus pairs and their retrieval are yet to reach their optimal levels. We propose that this observation can be explained by either the earlier maturation of the hippocampi or the integrative encoding hypothesis, according to which generalization is supported by a parallel neural network characterized by faster maturation.

We also conclude that migraine causes both basal ganglia- and hippocampus- associated learning impairments. Both pair acquisition and generalization performance of migraineurs were lower compared to healthy subjects. Our results support that these structures (or at least their functional networks) are affected by migraine without aura, and their structural impairments are manifest on a functional level as well.

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List of publications related to the subject of the thesis

I. BRAUNITZER G., **ŐZE A.**, EÖRDEGH G., PIHOKKER A., RÓZSA P., KASIK L., KÉRI S. NAGY A.
The development of acquired equivalence from childhood to adulthood—A cross-sectional study of 265 subjects.
PloS one, 12(6), e0179525. (2017), IF: 2.806

II. **ŐZE A.**, NAGY A., BENEDEK G., BODOSI B., KÉRI S., PÁLINKÁS É., BIHARI K., BRAUNITZER G.
Acquired equivalence and related memory processes in migraine without aura.
Cephalalgia, 37(6), 532-540. (2017), IF: 3.609

Further publications

BRAUNITZER G., **ŐZE A.**, NAGY T., EÖRDEGH G., PUSZTA A., BENEDEK G., KÉRI S., NAGY A.
The effect of simultaneous flickering light stimulation on global form and motion perception thresholds.
Neuroscience letters, 583, 87-91. (2014), IF: 2.030