Visual learning:
healthy development and the effects of migraine

PhD Thesis

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“Time moves in one direction, memory another. We are that strange species that constructs artifacts intended to counter the natural flow of forgetting.”

— William Gibson

List of publications providing the basis of the thesis

I. **The development of acquired equivalence from childhood to adulthood—A cross-sectional study of 265 subjects**

Braunitzer G., **Őze A.**, Eördegh G., Pihokker A., Rózsa P., Kasik L., Kéri S., Nagy A.

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II. **Acquired equivalence and related memory processes in migraine without aura**

Őze A., Nagy A., Benedek G., Bodosi B., Kéri S., Pálinkás É., Bihari K., Braunitzer G.

Cephalalgia, *37*(6), 532-540. (2017)

IF: 3.609

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List of abbreviations

AE: Acquired equivalence

ALER: Association phase learning error ratio

CA: Cornu Ammonis or Ammon's horn

CGRP: Calcitonin Gene Related Peptide

COVIS: COmpetition between Verbal and Implicit Systems

FC: Functional connectivity

fMRI: Functional magnetic resonance imaging

GER: Generalization error ratio

GPe, GPi: External and internal parts of the globus pallidus

ICHD-3beta: 3rd beta edition of the International Classification of Headache Disorders

MRI: magnetic resonance imaging

MTL: Medial temporal lobe

NAT: Number of acquisition trials

NSAID: Nonsteroidal anti-inflammatory drug

RAET: Rutgers Acquired Equivalence Test

RER: Retrieval error ratio

SN (SNr, SNc): Substantia nigra (pars reticulata and compacta)

SP: Substance P

STN: Subthalamic nucleus

VTA: Ventral tegmental area

1. Introduction

1.1. Learning and memory

Learning and memory are two basic functions of the nervous system that are essential to the full functioning and independent survival of both humans and animals (Kandel 2013). Either consciously or unconsciously, we use them in the vast majority of activities in our everyday life. These functions give us the ability to adapt better to our environment, and therefore they mean a huge evolutionary advantage.

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 (Kandel 2013). The two phenomena are difficult to separate. One could argue that such a separation is outright impossible at the functional level. Berry and Dienes (1991) examined whether implicit learning and implicit memory can be viewed as two functionally and stochastically independent phenomena. They found that the main characteristics of performance in implicit memory tasks apply to implicit learning tasks too. Thus they concluded that the two functions are not independent, and suggested that the same processes might be underlying the performance in these tasks (Berry and Dienes 1991). In addition, the same structures seem to play the key roles in both functions (Squire and Zola 1996, Packard and Knowlton 2002, Squire et al. 2004). In our opinion, learning and memory can be viewed as the two sides of the same coin, as they are complementary parts of the bigger phenomenon of memory. Learning is the process which allows memories to form, so it is at least to some extent analogous to the encoding process. Also, as we assess the efficiency of learning by examining memory, we consider the success of learning to be strongly dependant on the consolidation and retrieval processes. Taken these into account, we consider learning to be a subdivision of memory, thus in the next sections, we use the term *memory* in a way that is refers to the whole system (including learning), and the term *learning* denotes the process of knowledge acquisition.

1.2. The classification of memory

According to Atkinson and Shriffin (1968), memory may be divided into three systems: the sensory register, the short-term store and the long-term store. The sensory register stores the sensory information arriving from various inputs only for a brief time, after which this information decays. Short-term memory (also working memory) is the system that receives input from both the sensory register and the long-term store, and its functions are holding and manipulating information. The information stored here also decays completely, although in a longer time than the information in the sensory register (the timeframes are 30 seconds and one second respectively) (Atkinson and Shiffrin 1968). This modular model had been challenged by Baddeley and Hitch (1974), which led to the development of a new, more complex one. A new element, a central executive system, was introduced. The central executive system is connected to passive storages (where information is registered and subsequently fades or gets displaced) and active storages (which allow manipulation, i.e. continuous refreshing or update of information) (Baddeley and Hitch 1974). The elements of this system are distributed all across the neocortex, but the prefrontal cortex, especially the dorsolateral and ventrolateral prefrontal cortices, have a distinguished role (Kane and Engle 2002).

Finally, long-term memory is a permanent repository in which knowledge of a former state of mind is stored even after the given information has been out of conscious awareness for a long period of time (Kandel 2013). The information stored here is transferred from the short-term store. Viewed from the aspect of the consciousness of recollection, long-term memory can be divided into two systems: implicit and explicit memory (Graf and Schacter 1985).

Explicit memory

Explicit memory (also declarative memory) is the process that allows the conscious recollection of previously stored information (Kandel 2013). This system can be further divided into episodic memory and semantic memory, which are the subsystems for personal experiences (i.e. previous episodes of our lives, autobiographical memory) and for facts (i.e. general knowledge about the world, concepts, new words), respectively (Squire et al. 1993). 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. Therefore, changing surface characteristics or modality of stimuli has little to no effect on this type of memory (Berry and Dienes 1991, Squire et al. 1993, Kandel 2013). The learning realized via this system is fast, but forgetting and retrieval failure may occur.

Explicit memory is considerably homogenous both in a functional and structural sense. It is centered around the medial temporal lobe (MTL), with key structures being the hippocampal formation and adjacent cortices (Squire et al. 1993, Grafton et al. 1995, Hendelman 2006).

Implicit memory

Implicit memory (also nondeclarative memory) does not rely on conscious recollection, it is rather expressed through performance. In layman's terms, the pieces of knowledge acquired through this system are skills and information "we just come able to do or know"(Graf and Schacter 1985, Reber 1989, Squire et al. 1993, Squire and Zola 1996, Ellis 2009). The implicit system has been proposed as a kind of fine tuning of the perceptual-motor system through experience (Ungerleider et al. 2002)

Nondeclarative memory is anatomically diffuse and covers a diverse range of functions. It 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 (Berry and Dienes 1991, Squire et al. 1993). This means that this system is sensitive to modifications of conditions: changes in modality, surface characteristics (orientation, shading), or other alterations that require the subject to apply the implicit knowledge among new circumstances result in drastic decline of performance (Jacoby and Dallas 1981, Bassili et al. 1989). Finally, implicit memory has been described to be more robust as compared to explicit memory, thus it is less vulnerable to neurological insults (Schuchard and Thompson 2014). This characteristic is probably related to the anatomical diffuseness of the system (Squire et al. 1993), as well as to the fact that it relies on phylogenetically older, "more primitive" structures (e.g.. striatum, amygdala) than declarative memory (Reber 1989).

1.3. Implicit memory functions

Procedural learning

A wide range of memory functions are considered to be implicit. The most diverse group is procedural learning, which is basically the acquisition of a skill, habit or knowledge through repeated performance and practice, usually in a step-by-step and trial-and-error sense. It is, though, an umbrella term for a number of different forms of learning. It involves learning of various motor and perceptual skills, e.g. pursuit rotor task, mirror-drawing and -reading, and serial reaction time test (Cohen and Squire 1980, Heindel et al. 1989, Squire et al. 1993, Grafton et al. 1995, Reber and Squire 1998, Packard and Knowlton 2002), etc. Habit learning is considered to be based on nondeclarative memory too; it includes category learning (Knowlton and Squire 1993, Kéri 2003), artificial grammar learning (Knowlton and Squire 1996), probabilistic learning (e.g. weather prediction task) (Knowlton et al. 1994, Knowlton et al. 1996). Procedural learning depends on the intactness of the basal ganglia system, markedly of the neostriatum (Heindel et al. 1989, Knopman and Nissen 1991, Grafton et al. 1995, Knowlton et al. 1996). However, a growing body of evidence suggests that hippocampus also contributes to establishing these functions to some extent (Schendan et al. 2003, Turk-Browne et al. 2009, Shohamy and Turk-Browne 2013, Schapiro et al. 2014).

Priming

One of the most intensively studied implicit function is priming, which refers to an improved facility for detecting or identifying perceptual stimuli without conscious guidance or intention, based on previous experience with them (Squire et al. 1993). The priming effect, even if it shows decay, can be extraordinarily long-lasting: in one word fragment completion test significant differences between primed and unprimed words were still detected more than 16 months after a brief single encounter with a list of words (Sloman et al. 1988). Priming is mainly considered to be a function of the neocortex (Squire et al. 1993, Kandel 2013).

Conditioning

Conditioning, the act of connecting two stimuli by reward or punishment, is also thought to be implicit. While this type of learning was shown to require awareness in healthy humans (Marinkovic et al. 1989), experimental animals were still capable of learning of operant and

classical conditioned responses of the skeletal musculature or conditioned autonomic responses following hippocampus removal. Findings from humans with declarative system lesions also support that awareness is not always necessary for conditioning to occur (Squire et al. 1993). Simple classical conditioning and operant conditioning are linked to the cerebellum, amygdala and striatum (Squire et al. 1993, Packard and Knowlton 2002, Kandel 2013).

The classification of implicit and explicit memory functions and their neural correlates can be found in Figure 1.

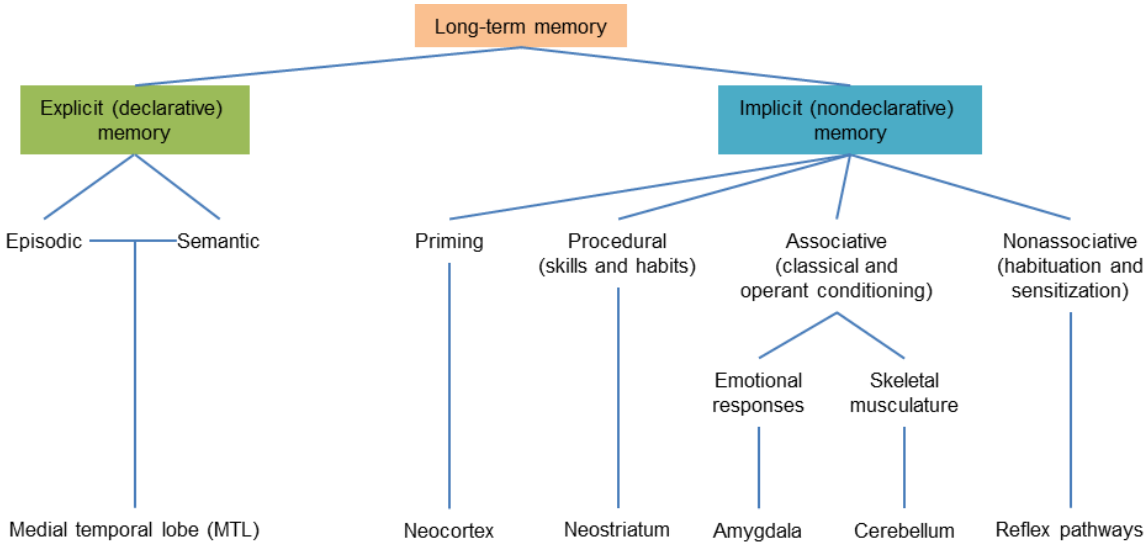

Figure 1.

The taxonomy of long term memory systems, and specific neural correlates. Based on Kandel et al, 2013.

1.4. Acquired Equivalence (AE)

Due to its importance in the studies presented here, one specific form of learning should be highlighted. Acquired equivalence (AE) is a learning paradigm, which tests both implicit and explicit learning. In this form of learning generalization is induced between two superficially dissimilar stimuli (referred to as antecedents) that have previously been associated with similar outcomes (referred to as consequents). In other words, subjects learn to that two or more stimuli are mapped onto the same outcomes or responses, thus they are equivalent in this sense (Meeter et al. 2009). Although it is often studied in animal learning paradigms, especially using pigeons (Edwards et al. 1982, Urcuioli and Lionello-DeNolf 2005, Urcuioli et al. 2006, Urcuioli and Vasconcelos 2008), this type of cognitive processing is also found in

humans (Goyos 2000, Myers et al. 2003, Meeter et al. 2009, Molet et al. 2013). 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 (or generalization) phase they had to apply this rule (i.e. transfer, generalize). Based on RAET performance of patients with different neurological disorders, the association phase is mediated mainly by the neostriatum, while generalization is thought to be a hippocampal function (Myers et al. 2003, Meeter et al. 2009).

1.5. Neural correlates of long term memory

The medial temporal lobe (MTL)

The principal structure of explicit memory is the hippocampal formation of the MTL. This phylogenetically old cortical area is rolled up deep within a fissure, intruding into the lateral ventricle. The formation consists of the three parts: the hippocampus proper (also called Ammon's Horn or cornu Ammonis, abbreviated CA) divided into four subfields termed CA1-CA4 that form the core of the hippocampal network; the dentate gyrus and the subicular region. (Squire et al. 1993, Hendelman 2006). The hippocampal formation has been described as an essential structure of explicit encoding, retrieval and of spatial memory as a cognitive map (O'keefe and Nadel 1978). This structure also processes information from all sensory modalities, including visual information (Squire et al. 2004), and has been proposed to be a key component of visual learning (Squire et al. 1993, Squire and Zola 1996, Squire et al. 2004). The hippocampus lies at the end of a hierarchical cortical processing network. The major source of its projections is the entorhinal cortex, which provides direct as well as indirect (through CA3) inputs to CA1. The entorhinal cortex, in turn, receives most of its cortical input from the adjacent perirhinal and parahippocampal cortices. The projections to these cortices originate in unimodal and polymodal areas in the frontal, temporal, and parietal lobes, as well as in the retrosplenial cortex (Figure 2.). From the aspect of visual modality, the perirhinal and parahippocampal cortices have distinguished importance, receiving input from unimodal and dorsal stream visual areas respectively (Squire et al. 1993, Squire and Zola 1996, Malkova and Mishkin 2003, Squire et al. 2004).

Further structures associated with declarative memory include the prefrontal cortex (Ofen et al. 2007), the inferior temporal cortex (Squire and Zola 1996) and the medial thalamus (Mayes 1995).

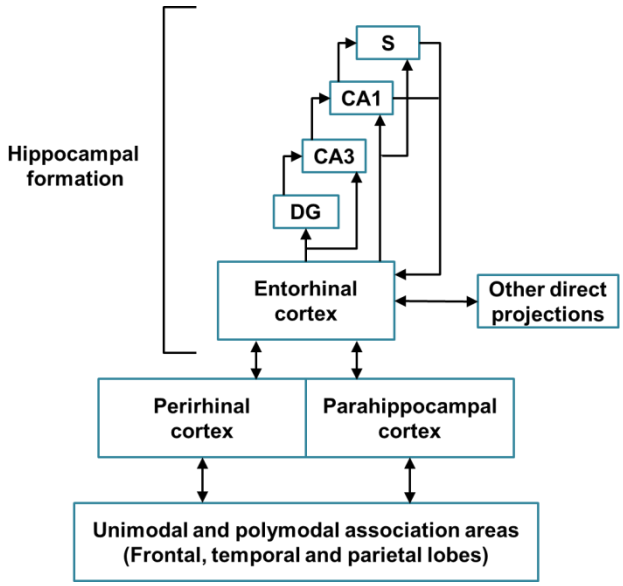

Figure 2.

The organization of the explicit system. Abbreviations: DG: dentate gyrus; CA: ammon's horn; S: subiculum. After Squire et al, 2004.

The basal ganglia

The basal ganglia comprise several interconnected subcortical nuclei, namely the caudate nucleus and putamen (together forming the neostriatum), the external and internal segments of globus pallidus (GPe and GPi), substantia nigra (SN) pars reticulata (SNr) and compacta (SNc), and the subthalamic nucleus (STN). The basal ganglia function primarily in cortico-basal ganglia-thalamo-cortical loops (Alexander et al. 1986, Alexander and Crutcher 1990), but loops of subcortical origin has been described as well (McHaffie et al. 2005). Caudate body, alongside with STN serves as the main input structure of the basal ganglia, getting direct glutamatergic afferents from all around the cerebral cortex (Parent and Hazrati 1995) and indirect projections from various subcortical structures through the thalamus (i.e. superior and inferior colliculus, periaqueductal grey and other midbrain and hindbrain structures) (McHaffie et al. 2005). The two basal ganglia input structures then relay signals, via direct and indirect routes, to the principal output nuclei, namely, the GPi and the SNr. These nuclei then project either directly to the thalamus, midbrain and medulla, or indirectly via thalamus

to cortical and limbic regions from which the input to the system originated. Detailed circuitry of the basal ganglia can be found in Figure 3. (Alexander and Crutcher 1990, Nambu 2008).

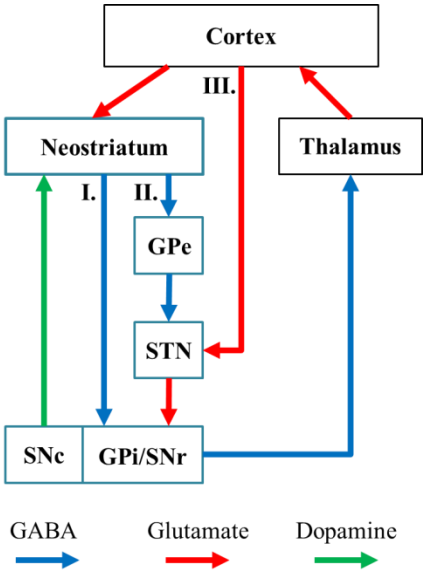

Figure 3.

The structure of the basal ganglia circuitry. Abbreviations: GPe, GPi: external and internal part of globus pallidus; SNr, SNc: substantia nigra pars reticularis and compacta; STN: subthalamic nucleus. The roman numbers indicate the three main routes (I: Direct or "Go" pathway, II: Indirect or "non-Go" pathway, III: hyperdirect pathway) of the circuitry.

The basal ganglia form separate circuits with distinct roles. Although these are organized in a parallel manner, the cortico-basal ganglia loops should be viewed more as a continuum rather than subdivisions with strict boundaries (Nambu 2008). Motor circuits and oculomotor circuits have important roles in the focused selection of skeletal muscle movements and regulating the saccadic eye movements (Hikosaka and Wurtz 1989), respectively. The dorsolateral prefrontal circuit provides direct connection between the dorsolateral caudate and the prefrontal cortex. The lateral orbitofrontal circuit originates in auditory and visual association areas and projects to the ventromedial caudate. Lastly, the anterior cingulate circuit connects limbic structures (including hippocampus, amygdala, entorhinal and perirhinal cortices) with the ventral striatum. The latter three circuits have been described to take part in various procedural learning functions (Alexander et al. 1986, Packard and Knowlton 2002, Nambu 2008). In addition, the basal ganglia play an important role in reward-driven mechanisms, with the dopaminergic SN-striatum connection, alongside with the ventral tegmental area (VTA) - hippocampus pathway (Delgado 2007).

1.6. The relation of implicit and explicit systems

The question of the relationship between declarative and nondeclarative memory is still a subject of on-going debate. Conflicting findings and views yielded several models. One of these, the sensitivity hypothesis, assumes a single memory system with a single source of retrievable information, probably of explicit origin. It postulates that the task-relevant decision processes are guided mainly by explicit memory, and implicit and explicit tests are simply differentially sensitive to detecting group differences (Shanks and John 1994, Shanks 2005). The finding that patients with MTL lesion perform worse not only in explicit but also implicit memory task provides evidence for this view (Shanks and John 1994, Reber and Squire 1998, Shanks 2005). However, the hypothesis cannot account for the selective memory deficits following neurological disruptions of the related systems. Another concept describes implicit and explicit memory to be separate systems that work in parallel (the multiple memory systems hypothesis). Human, monkey and rat lesion studies of structures associated with the declarative and nondeclarative memory provided evidence for this model (Scoville and Milner 1957, Corkin 1984, Heindel et al. 1989, Packard et al. 1989, Knopman and Nissen 1991, Rempel-Clower et al. 1996, Squire and Zola 1996). Some propose the two systems to be functionally independent (Berry and Dienes 1991, Reber and Squire 1998). However, there are fMRI findings of significant hippocampal activation in implicit learning, which contradicts the idea of total functional independence (Schendan et al. 2003, Turk-Browne et al. 2009, Hannula and Greene 2012, Shohamy and Turk-Browne 2013). The cooperative activation of the two systems can have a facilitative effect: performance on certain implicit tasks (e.g. serial reaction time task, statistical learning, contextual cueing) were found to increase when aided by concurrent explicit activation (Hannula and Greene 2012, Shohamy and Turk-Browne 2013, Schapiro et al. 2014). Competition between the two systems has also been described in several human studies using psychophysics and imaging techniques, with results showing that explicit activation negatively correlated with implicit activity (Diamond et al. 1994, Packard and Knowlton 2002, Rieckmann and Bäckman 2009, Rieckmann et al. 2010, Ashby et al. 2011, Huang-Pollock et al. 2011). A more complex network has also been proposed by Sun and colleagues, which describes an action and non-action centred representation in both systems. According to the model, the four subsystems adapt from trial to trial, with the explicit system generating rules online as the implicit system feeds information to it, and thus can implement rule- based transfer (Sun et al. 2005).

1.7. Functional results of disruptions to the explicit and implicit systems

The central role of MTL in memory was discovered following the well-known case of H.M., a patient who underwent a bilateral medial temporal lobectomy (removal of the hippocampal formation, parahippocampal gyrus and entorhinal cortex) to treat his severe temporal epilepsy. The operation solved his epilepsy, but he was left with profound anterograde amnesia. The memory disorder did not affect the working memory (he performed on normal level), nor his IQ, his recollection of the events preceding the operation had only mild deficits (he had retrograde amnesia limited to one- to two-year period before surgery). However, the explicit learning functions were seriously impaired. In contrast nondeclarative memory functions (e.g. serial reaction time test, mirror drawing, mirror reading) were spared (Scoville and Milner 1957, Corkin 1984, Squire et al. 1993, Corkin et al. 1997).

Examination of other amnesiacs showed that the nature and extent of lesion is related to the severity of the functional deficit. Isolated bilateral CA1 damage led to only moderate anterograde and minimal retrograde amnesia, while concurrent damage of CA1, CA2, CA3, dentate gyrus and entorhinal cortex resulted in severe anterograde and extensive retrograde amnesia (Zola-Morgan et al. 1986, Rempel-Clower et al. 1996). Lesion studies conducted on rats (Packard et al. 1989) and monkeys (Squire et al. 1993, Squire and Zola 1996, Malkova and Mishkin 2003) support these findings: damage to the hippocampal formation, fimbria, fornix, prefrontal cortex, and inferior temporal cortex all cause explicit memory disruptions of varying extent. The hippocampal atrophy of Alzheimer's patients cause marked decline in explicit functions as well (Heindel et al. 1989, Fox et al. 1996). Both amnesiacs and Alzheimer's patients were generally found to perform well in implicit tasks, they had no problem with category learning (Knowlton and Squire 1993, Kéri et al. 1999), probabilistic classification learning (Knowlton et al. 1994), artificial grammar learning (Knowlton and Squire 1996) the implicit part of a serial reaction time task (Reber and Squire 1998) and motor learning tasks (Heindel et al. 1989). Yet these patients failed in tests assessing declarative memory, and could not verbalize the rules of the various tasks. Furthermore, healthy subjects outperformed these patients when trial numbers were high enough for an explicit knowledge of the underlying rules to develop (Knowlton et al. 1994).

Conditions that damage the basal ganglia (e.g. Huntington's and Parkinson's disease) give rise to implicit deficits, with preserved explicit memory (Heindel et al. 1989, Knopman and Nissen 1991, Packard and Knowlton 2002, Wilkinson et al. 2009). Patients with disorders

affecting the basal ganglia had a hard time completing implicit tasks, but no problem recalling or applying explicit rules. Huntington's disease patients were shown to perform poorly on serial reaction time task (Knopman and Nissen 1991), motor learning tasks (Heindel et al. 1989), and mirror reading (Squire et al. 1993). Parkinson's disease patients, on the other hand, show more diverse results, as Parkinson's disease often leads to dementia in later stages of illness. Non-demented Parkinson patients showed weaker performance in probabilistic classification (Knowlton et al. 1996), category learning (Squire et al. 1993), and sequence learning (Rieckmann and Bäckman 2009), while still able to reach the normal level in motor learning (probably a result of the robustness of the nondeclarative system) (Heindel et al. 1989). Demented Parkinson's disease patients had poor results in both explicit and implicit tasks (Heindel et al. 1989, Wilkinson et al. 2009).

Performance in the RAET paradigm (consisting of an association and generalization phases which assess striatal and hippocampal function, respectively) has been examined in neurological conditions involving the basal ganglia and the hippocampi. 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 (Myers et al. 2002, Myers et al. 2003, Bódi et al. 2009).

1.8. Memory across the lifespan

The development and aging of the hippocampus and the caudate nucleus

Structures associated with declarative memory show a significant development in the first years of life. In an MRI study, Utsunomiya (1999) found that the volume of the hippocampal formation increased sharply during the first 2 years of life (however, it must be noted that compared to the increase of the total brain volume it is a decrease), then continued to grow at a more moderate pace, reaching the peak volume in preadolescence (9-11 years). Other studies confirmed this developmental trajectory (Giedd et al. 1996, Knickmeyer et al. 2008, Uematsu et al. 2012, Hu et al. 2013). Following this, the volume of hippocampus is relatively preserved until 60 years of age, after which volume loss is observed (Grieve et al. 2005, Raz et al. 2005). The prefrontal cortex, on the other hand, shows development well into the late

adolescence (Gogtay et al. 2004, Sowell et al. 2004, Ofen et al. 2007), but starts to shrink from early adulthood by 5-10% per decade (Grieve et al. 2005, Raz et al. 2005).

The caudate nucleus is thought to be quite mature already at birth (Clohessy et al. 2001), but shown to grow rapidly in the first two years as well (Knickmeyer et al. 2008), reaching peak volume at the age of 10-14 years (Lenroot et al. 2007). During the later lifespan, starting from early adulthood, decrease in striatal volume was reported. This tendency was found to be linear and up to 10% per decade (Raz et al. 2003, Raz et al. 2005).

Functional development

Hayne and colleagues (2000) demonstrated that one-year-old children perform significantly worse in an explicit task than children of 18 months. Other studies also demonstrated marked increase in explicit performance during the first years of life (Diamond et al. 1994), which continues in later years of childhood into adolescence (Ofen et al. 2007, Huang-Pollock et al. 2011, Ofen 2012). As major volumetric changes in the hippocampus are over by the age of 2 to 3 years (Giedd et al. 1996), this trajectory might be driven by the prolonged development of prefrontal cortex (Ofen 2012).

Compared to the explicit system, the implicit system seems to mature earlier functionally as well (Casey et al. 2004). Saffran and colleagues (1999) found that 8-month-old infants were already capable of completing a statistical learning task. Children as young as 4 months of age were found to be able to learn simple sequences of visual stimuli, and 18- month-olds could learn more complex sequences as well (Clohessy et al. 2001). Others did not find any age related changes in motor-learning and sequence learning performance (Meulemans et al. 1998, Vinter and Perruchet 2000, Vinter and Perruchet 2002). Likewise, Thomas and Nelson (2001) found no significant differences in sequence learning performance between 4-, 7-, and 10-year-old children and adults. However, in another study of the same group using a similar task, it was found that adults to outperform children, probably due to the adults being faster in developing explicit knowledge on the task (Thomas et al. 2004). Minda and colleagues (2008) found that children of various ages (3,5 and 8 years) could perform on the same level as adults in implicit tasks. Explicit performance, on the other hand, was found to be age-dependent.

Functional changes in aging

The decline of both episodic and semantic memory performance is already apparent by the age of 50, a tendency which grows stronger as age advances (Rönnlund et al. 2005). In contrast, implicit functions are well preserved until an older age despite the considerable structural decline of the caudate nucleus: decrease in performance only starts to appear around 70 years of age (Rieckmann and Bäckman 2009, Rieckmann et al. 2010, Simon et al. 2011, Simon and Gluck 2013). Older adults were found to underperform young adults in probabilistic learning task and serial reaction time task as well (Rieckmann et al. 2010, Dennis and Cabeza 2011, Simon et al. 2011). A study investigating the RAET task performance in aging showed that young adults achieve better results in both the association and generalization phases. A marked decrease in generalization performance was found in the oldest group (above 70 years) (Simon and Gluck 2013).

A notable difference in the effect of the two systems on each other in young and old people has been described. In young adults explicit learning does not interfere with implicit learning (Willingham and Goedert-Eschmann 1999, Song et al. 2007), on the contrary, it can even facilitate it (Howard and Howard 2001). In older adults, on the other hand, explicit knowledge was found to hinder implicit learning (Howard and Howard 2001). These findings may reflect a processing capacity limit, which is exceeded by simultaneous explicit and implicit processing demands in older adults (Rieckmann and Bäckman 2009). Functionally, the striatum and MTL of young adults was found to be activated in parallel, in a competitive way: during implicit tasks, the initial activity in MTL gradually decreases as the striatal activity increases. In older adults, both MTL and striatum activated. Older adults may rely more heavily on the activation of MTL and other cortical structures to compensate for the age-related decline in striatal functions. The compensatory processes can deplete when explicit system resources are under greater load, such as when task complexity is increased or explicit information is introduced (Rieckmann and Bäckman 2009, Rieckmann et al. 2010).

1.9. Migraine: definition, characteristics and epidemiology

Migraine is a common chronic neurological condition, one of the primary headaches. The 3rd beta edition of the International Classification of Headache Disorders (ICHD-3beta) by the International Headache Society (International Headache Society 2013) lists 21 altered health

states as migraine or conditions associated with migraine (including probable migraine, complications of migraine and episodic syndromes that may be associated with migraine), with the most common being migraine without aura. Migraine has a remarkably high prevalence: it is estimated to be, around 10 to 12 % in Western countries (Breslau and Rasmussen 2001), reaching peak incidence at the age of 15-17 in females and around 10-11 years in males (Lipton and Bigal 2005). The importance of this disease is further emphasized by its remarkably high prevalence and the severity of disability caused by it (Murray et al. 1996, Lipton and Bigal 2005, International Headache Society 2013). As our studies discussed in this thesis are limited to migraine without aura, from this point onwards we are going to refer to this condition simply as migraine.

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 (International Headache Society 2013).

1.10. The pathophysiology of migraine

Despite migraine being one of the most studied neurological disorders, the exact aetiology has still not been clarified. There are two prevailing theories on what causes the onset of the episodes. The vascular hypothesis postulates that the sources of the attack are the perivascular nociceptors surrounding the major cerebral blood vessels, while the neurogenic hypothesis attributes the onset to neuronal events in the brain (Parsons and Strijbos 2003, Olesen et al. 2009).

On what most studies seem to agree is that the trigeminovascular system plays a key part in the process (May and Goadsby 1999, Parsons and Strijbos 2003, Goadsby 2005, Goadsby et al. 2009, Olesen et al. 2009). We have known for over 70 years that the stimulation of the dura mater, the large cerebral vessels and sinuses causes strong, deep, ipsilateral headache and nausea (Ray and Wolff 1940). Balloon distension of these structures causes similar symptoms (Parsons and Strijbos 2003, Olesen et al. 2009). The dura and the blood vessels are innervated

by a plexus of largely unmyelinated fibers that arise from the ophthalmic division of the trigeminal ganglion and from the upper cervical dorsal roots of the spinal cord (Penfield and McNaughton 1940, Goadsby et al. 2009). The related neurons in the trigeminal ganglion contain substance P (SP) and calcitonin gene related peptide (CGRP), both having a vasodilatatory effect as well as an important role in inflammation and pain transmission (Dray 1995). The headache is probably caused by a combination of several factors. First, vasodilatation occurs in the cerebral and dural vessels, possibly caused by CGRP (Goadsby 2005). CGRP and SP cause sterile inflammation and plasma protein extravasation that can sensitize the nerve endings (Markowitz et al. 1987, Goadsby et al. 2009). Beside these, mast cell degranulation and platelet aggregation may also have a role in this respect (Dimtriadou et al. 1991, Dimitriadou et al. 1992). Second, the endogenous pain control pathways show a subnormal activity (Welch et al. 2001, Goadsby et al. 2009), and a central sensitization occurs, affecting both the intracranial vessels and peripheral structures (Olesen et al. 2009). It must be noted, though, that there is no agreement on the relevance of the vasodilatation. Some studies using nitroglycerine to evoke migraine headache and imaging techniques to measure vascular diameter did not identify significant changes neither in cerebral artery diameters, nor in cerebral blood flow during the attacks (Schwedt and Dodick 2009). While the overwhelming majority of the related studies agree that vasodilatation is an important element, these findings raise the possibility that changes in vascular diameters might be transient, or might not be necessary for the development of all migraine headaches.

Beyond the alterations affecting the circulation of the brain, several findings show disturbances in the ion homeostasis. Magnesium (Mg^{2+}) levels, in particular, seem to be affected in migraine. Levels as low as 20 to 30% of control have been reported in both the brain and the serum (Schoenen et al. 1991, Welch and Ramadan 1995). These findings have been confirmed in women with menstrual migraine (Mauskop et al. 2002). The role of Mg^{2+} is well-established in a wide range of cellular processes (among others: enzyme systems, bioenergetics, calcium and potassium currents, serotonin receptor activity, platelet aggregation and release of inflammatory-pain mediators), and its low level is associated with hyperexcitability, increased vascular reactivity to serotonin and cerebrovascular constriction. Thus, this shift in Mg^{2+} is likely to play a role in migraine pathophysiology (Welch and Ramadan 1995, Mauskop et al. 2002). Evidence of hyperexcitability have indeed been observed, though not in relation with Mg^{2+} levels (Antal et al. 2005).

1.11. The effect of migraine on the brain

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 (Rocca et al. 2006, Schwedt and Dodick 2009, Liu et al. 2013). Schmidt-Wilcke et al. (2008) has also found significant decrease in grey-matter in pain related regions, but not in areas specific to migraine in the brainstem. It has been postulated that these grey matter changes are the consequence of frequent nociceptive input, therefore they should be reversible when migraine attacks cease. These findings are consistent with observations that chronic pain can indeed cause such reversible alterations (May 2008, Rodriguez-Raecke et al. 2009). A significant increase of hippocampal and caudate grey matter volumes was discovered in low-frequency migraineurs. This possibly might be due to initial adaptive structural plasticity caused by the higher amount of sensory input these structures receive during migraine attacks. However, with the rise of the attack numbers, the volumes of these areas appear to decrease, i.e. high-frequency migraine patients had comparable values to healthy controls (Maleki et al. 2011, Maleki et al. 2013).

The findings concerning white-matter changes are less conclusive. While Liu and colleagues (2013) found no significant change of white-matter in a one-year follow-up MRI study, others describe deep white-matter lesions (Schwedt and Dodick 2009). The possibility of atrophy and axon loss was raised as well (Rocca et al. 2006).

An increased prevalence of stroke was also found in migraine patients (Etminan et al. 2005). The majority of these lesions were present in the posterior circulation territory, localised mainly infratentorially, typically in watershed-zones of the cerebellum (Kruit et al. 2004, Kruit et al. 2005, Schwedt and Dodick 2009). The lesions were subclinical, the examined patients did not report a history of stroke or transient ischemic attack, nor had relevant abnormalities at standard neurological examination (Kruit et al. 2004).

fMRI studies also found several significant alterations in migraineurs (Schwedt et al. 2015). An fMRI study conducted by Gao found a decrease in the intraregional functional connectivity (FC) density of several brain regions. Among the affected regions were frontal structures (prefrontal cortex, anterior cingulate cortex and insula), the hippocampus and nuclei of the basal ganglia system (the caudate nucleus and putamen). In addition, the disease duration was found to correlate with the decrease of FC density in the prefrontal cortex,

caudate nucleus and putamen, implying that the repeated migraine attacks might consistently affect the resting-state FC architecture of these areas over time (Gao et al. 2016). These findings seem to correspond with the ones of Maleki and his colleagues (2011, 2013), who compared low- and high- frequency migraineurs and described a significantly lower FC of both the caudate nucleus and the hippocampi in high frequency migraine.

Furthermore, increased iron deposition could be observed in the periaqueductal grey-matter, putamen, globus pallidus, the severity of which also positively correlated with longer disease duration (Welch et al. 2001, Kruit et al. 2009).

It can be seen that migraine gravely affects a wide range of brain areas, including the hippocampus and the basal ganglia. With these structures playing key parts in different learning functions, the question rises whether damage to them causes any impairment of learning that is detectable using functional tests.

1.12. Migraine and learning

Functional studies of migraineurs' learning are scarce and findings have been somewhat contradictory. Mulder and colleagues (1999) did not find any difference between controls and migraineurs without aura in tests assessing a wide range of cognitive, memory and learning functions. Le Pira and his colleagues (2000), on the other hand, found that migraine patients performed worse in attention tests as well as in verbal and nonverbal recall tests. Decline in motor speed and tactile perception was reported, too (Ravishankar and Demakis 2007). Others found no change in intelligence and explicit memory performance (Pearson et al. 2006, Paemeleire 2009, Rist et al. 2012). One study mentions, however, that lower level cognitive processes, particularly as assessed by visual tasks, may be vulnerable to migraine (Pearson et al. 2006).

In summary, despite the notable lesions, patients suffering from migraine show only mild to moderate cognitive difficulties or none at all. It seems that the plasticity of the brain is capable to prevent structural changes from becoming manifest on a functional level. It must be noted, though, that most of these tests monitor only the performance of declarative memory, to be more specific, primarily the retrieval function of the explicit system, which depends on the

hippocampi to a variable extent. Therefore, it is possible that with tests that target the basal ganglia and the hippocampi, of functional decline would show more markedly.

2. 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, to provide data on the functional development of the associated structures. We also intended to investigate if migraine causes any changes of performance in these learning functions.

The specific aims of the study were:

- to describe the age-related development of the basal ganglia- and hippocampus-associated learning functions in healthy humans from childhood to adulthood in a specific learning paradigm (Rutgers acquired equivalence test)
- to examine if any sex-related differences exist in the development of the above mentioned functions
- to compare the basal ganglia- and hippocampus- associated learning functions of migraineurs and healthy subjects.

3. Materials and methods

3.1. Participants

All subjects were of Caucasian race and of similar socioeconomic status (middle class). Only patients with negative history of ophthalmological, neurological and psychiatric conditions were eligible for the study. Intactness of colour vision was tested by Isihara plates prior to testing. Before volunteering the potential subjects were informed about the background and goals of the study, as well as about the procedures involved. In case of underage subjects parents were also informed. It was also emphasised that given the lack of compensation or any direct benefit, the participants were free to quit at any time without any consequence (no one elected to do so). Those who decided to volunteer signed an informed consent form. When minors were assessed, their parents signed the informed consent form, as required by the Hungarian law; however a verbal consent was also collected from the children before the beginning of testing. Both study protocols conformed to the tenets of the Declaration of Helsinki in all respects, and it was approved on several occasions 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. The final sample size and the size of the subsamples were determined by the number of volunteering subjects in the 2 years of data collection. The basic demographics of the subjects along with their distribution in cohorts (see 3.4.) can be found in table 3.

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 sample size was limited by the timeframe (6 months) and the rigorous application of the diagnostic and inclusion/exclusion criteria. From the 37 migraine patients that were approached in the study period 10 were excluded because they had migraine with aura (or attacks both with and without aura), 3 had other neurological condition(s), and in one case psychiatric comorbidity was present. One patient dropped out because of computer failure at the end of the association phase.

12 of the 22 patients received interval therapy. For this purpose 10 patients took flunarizine at a dose of 10 mg/day, one parient used topiramate (25 mg/day) and another one mitrazapine (15 mg/day). 10 patients received no interval therapy. Abortive medications were used by all patients. These were dominantly sumatriptane and NSAIDs (ibuprophen, naproxen, diclofenac sodium, metamizole sodium, indomethacin). Two patients also used ergotamine tartarate for abortive purposes.

The control group consisted of 22 healthy volunteers matched to the migraineur group in sex, age and level of education ($n_{ELEMENTARY}$=3, $n_{SECONDARY}$=10, n_{HIGHER}=9 in both groups). 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. Given the small sample size, potential control subjects were approached personally. None of them declined participation.

The basic demographic and migraine-specific characteristics of the study and control groups are summarized in Table 1.

	n	Age (years)	Sex ratio (female:male)	Migraine history (years)	Attack frequency per month	Estimated total number of attacks
Controls	22	44.0 (21-51)	20:2	n/a	n/a	n/a
Migraineurs	22	42.5 (20-52)	20:2	15.64 (10.9)	5.0 (4.8)	414 (18-4000)

Table 1.
Demographic and migraine characteristics of the participants

3.2. Materials

The 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 authors. 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.

3.3. 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 (A1, A2, B1, B2) and four possible fish of different colours (X1, X2, Y1, Y2), referred to in the terminology of Myers and colleagues (2003) as antecedents and consequents, respectively. The four possible faces were: a male adult, a male child, a female adult and a female child. The four colours were: red, green, blue and yellow. 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 and a generalization (or transfer) phase.

To illustrate the process in simple terms: let us assume that the male child (A1) and the female adult (A2) are first associated with the green fish (X1), while the female child (B1) and the male adult (B2) are associated with the red fish (Y1). These are the shaping and equivalence training parts of the association phase. This way, the male child and the female adult become associated through the green fish (A1, A2 → X1), and the female child and the male adult

through the red fish (B1, B2 → Y1). In the next step of the association phase, new consequents are introduced: the participant learns that the male child (A1) and the female child (B1) are also associated with the yellow fish (X2) and blue fish (Y2) respectively. If the equivalence of stimuli has been successfully learned, the participant should be able to generalise that the female adult (A2) is associated with the yellow fish (X2) and the male adult (B2) is associated with the blue fish (Y2). This is what the generalization phase seeks to test. A formal summary of the process is given in Table 2.

TRAINING (ACQUISITION)			**TESTING**
Association Phase 1: Shaping	**Association Phase 2: Equivalence Training**	**Association Phase 3: New Consequents**	**Generalisation Phase: Equivalence testing**
A1 → X1	A1 → X1	A1 → X1	
	A2 → X1	A2 → X1	A2 → X2?
		A1 → X2	
B1 → Y1	B1 → Y1	B1 → Y1	
	B2 → Y1	B2 → Y1	B2 → Y2?
		B1 → Y2	

Table 2.

The summary of the Rutgers Acquired Equivalence Test (after Myers et al, 2003). A and B stand for antecedents, X and Y stand for consequents. Testing phase also included retrieval trials, where recall of previously learned pairings were tested.

While the formal description may make the impression that the task is a difficult one, in fact, healthy children (Goyos 2000) and also mentally retarded individuals (Dube et al. 1987, de Rose et al. 1988) reliably make this kind of generalisation.

The participants' task throughout the association and generalisation phases was to indicate their choice in each trial by pressing one of two keyboard buttons labelled LEFT and RIGHT. A screenshot of a trial from the paradigm can be found in Figure 4. The correct key was uncorrelated with the fish, that is, participants learned that a given face was associated with a fish of a given colour, and not a given key. Visual feedback on the correctness of choice was provided in the association phase but not in the generalization phase. 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 (4 after the presentation of the first association, and 4, 6, 8, 10, 12 with the introduction of each new association, respectively) to be allowed to proceed. This meant an elevated number of the required consecutive correct trials compared to the original paradigm, which made getting through the association phase by mere guessing less probable. Similarly, in the generalization phase there were 48 trials (12 trials of new and 36 trials of previously learned associations), as opposed to the 16 trials of the original paradigm. From this also follows that the length of the association phases varied among the participants, depending upon how efficiently they learned. The generalisation phase, in contrast, always contained 48 trials (12 trials of new and 36 trials of previously learned associations) as opposed to the 16 trials of the original paradigm.

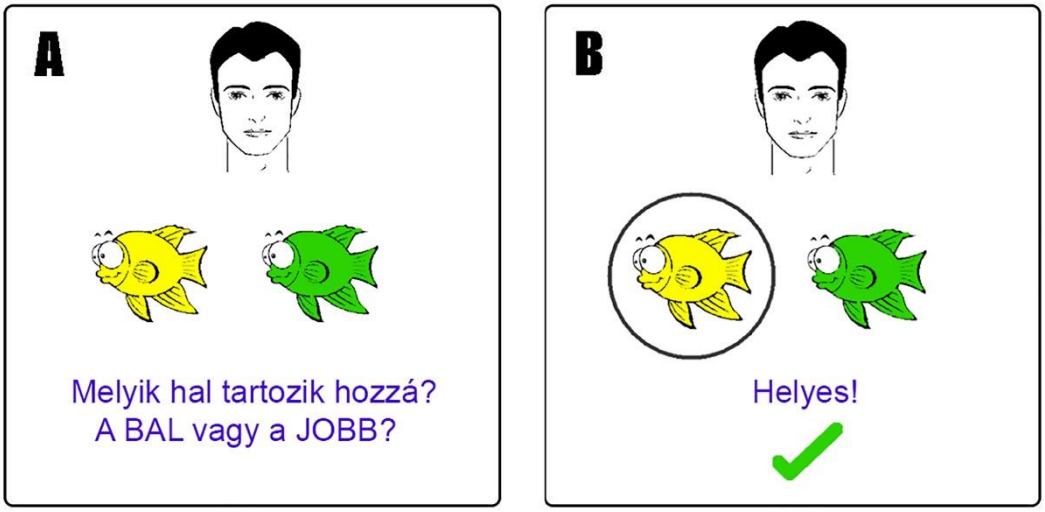

Figure 4.

Two screenshots of trials from the paradigm. Each trial contained an antecedent stimulus (face) and two possible consequents (fishes). A: Translation of the text: Which fish goes with this face? LEFT or RIGHT? B: Visual feedback on the correctness of the answer (provided only during association phase).

3.4. Statistical analysis

Study #1

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) (Faul et al. 2009). The results were analyzed in three groups: results from the association phase,

results from the "old associations" part (i.e. when the participant was presented an already learned association), and the “new associations” part (i.e. previously not learned associations) of the generalisation phase. The number of correct and wrong answers was recorded in all phases, and the ratio of these numbers was calculated for every phase. The number of trials necessary for the completion of the association phase was also recorded. For further analysis participants were distributed in 14 cohorts based on age. Cohort 0 involved kindergarten children (3 to 6 years of age), cohorts 1 to 8 corresponded to the grades of the elementary school (7 to 14 years of age), cohort 9 involved high school students (15 to 19 years of age), and cohorts 10-13 involved adults aged 20 to 29, 30 to 39, 40 to 49, and 50+, respectively. The kindergarten cohort was not divided into further subgroups because of the small number of subjects (n= 12), and the high school cohort was dominated by seventeen-year-olds to such an extent that it would have made no sense to create subgroups. The basic demographics of cohorts can be found in Table 3. The results were analysed with factorial analysis of variance (ANOVA). Sex and cohort were selected as predictors. Achieved power was calculated in G*Power (Universität Düsseldorf, Germany) (Faul et al. 2009).

Cohort	n	n_{male}	n_{female}	Mean age(years)
0	12	6	6	4.17
1	18	10	8	7.15
2	14	6	8	8.43
3	22	11	11	9.60
4	12	7	5	10.50
5	18	10	8	11.53
6	17	10	7	12.52
7	17	10	7	13.59
8	21	13	8	14.62
9	41	16	25	16.76
10	27	6	21	24.11
11	17	4	13	34.06
12	23	4	19	45.30
13	6	3	3	50.67

Table 3.

The distribution of the participants in cohorts, and basic demographics.

Study #2

The four groups of analysis were the same as in Study #1: the number of trials needed for the completion of the association phase and the error ratios of this phase, as well as error ratios of "old" and "new" associations in the generalization phase were compared in migraineurs and controls using SPSS 21.0 (IBM, USA). 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) had effect on the target variables in the migraine group (error rates and the number of association phase trials). The effect of interval therapy as a chronic influence (and thus a potential confounder) was also tested.

4. Results

4.1. Study #1

The achieved power for the factorial ANOVA was 0.88 (f= 0.25, α= 0.004, sample size= 265, number of groups= 14). Cohort-wise performance means by the studied parameters are given in Table 4.

Cohort	NAT	ALER	RER	GER
0	122.33 (63.66)	0.31 (0.15)	0.29 (0.16)	0.40 (0.20)
1	56.78 (11.21)	0.10 (0.05)	0.10 (0.16)	0.18 (0.23)
2	69.00 (42.28)	0.09 (0.08)	0.05 (0.10)	0.14 (0.28)
3	71.91 (35.49)	0.15 (0.20)	0.05 (0.09)	0.14 (0.28)
4	59.75 (18.30)	0.08 (0.06)	0.06 (0.09)	0.19 (0.26)
5	71.28 (62.61)	0.09 (0.14)	0.09 (0.15)	0.20 (0.28)
6	85.59 (54.27)	0.12 (0.11)	0.09 (0.09)	0.24 (0.28)
7	69.88 (57.68)	0.10 (0.12)	0.11 (0.19)	0.27 (0.32)
8	89.24 (75.09)	0.12 (0.12)	0.11 (0.15)	0.21 (0.28)
9	63.54 (22.40)	0.09 (0.09)	0.05 (0.07)	0.16 (0.26)
10	59.93 (11.69)	0.07 (0.04)	0.04 (0.08)	0.24 (0.34)
11	53.59 (10.24)	0.05 (0.03)	0.01 (0.01)	0.21 (0.31)
12	59.74 (14.67)	0.08 (0.05)	0.05 (0.05)	0.18 (0.28)
13	79.67 (33.82)	0.13 (0.07)	0.06 (0.09)	0.03 (0.04)

Table 4.

The performance means of the cohorts. Abbreviations: NAT: number of acquisition trials; ALER: association learning error ratio; RER: retrieval error ratio; GER: generalization error ratio. Values are given as mean (SD)

Number of acquisition trials (NAT)

The factorial ANOVA analysis of this parameter with cohort and sex as covariates yielded the following results: 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). A Tukey's post-hoc analysis was conducted on cohort to find out about the source of the significant overall variance. The post-hoc analysis revealed that cohort 0 differed significantly from all other cohorts at different levels of probability (p= 0.05- 0.001).

That is, kindergarten children needed significantly more trials to acquire the associations than members of any of the other cohorts. The results are summarized in Figure 5.

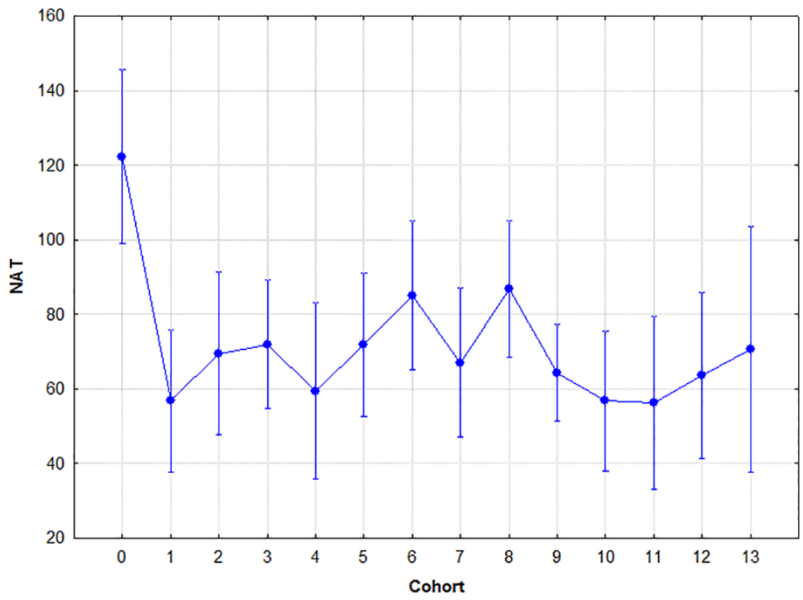

Figure 5.

The mean number of trials needed to acquire the associations by cohort.
Circle: mean; whiskers: ±SD.

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). A Tukey's post-hoc analysis was conducted on cohort to find out about the source of the significant overall variance. The post-hoc analysis revealed that cohort 0 differed significantly from all other cohorts at $p< 0.001$. In other words, kindergarten children made significantly more mistakes during acquisition than members of any of the other cohorts, and no significant differences were found among the rest of the cohorts. The results are summarized in Figure 6.

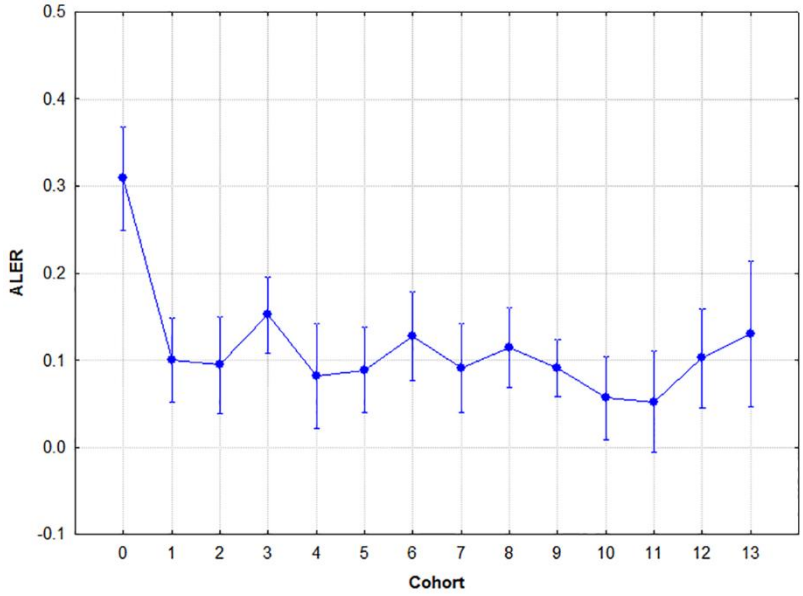

Figure 6.

Mean association learning error ratios by cohort.
Circle: mean; whiskers: ±SD.

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). A Tukey's post-hoc analysis was conducted to find out about the source of the significant overall variance. The post-hoc analysis revealed that cohort 0 differed significantly from all other cohorts at p< 0.001. This means that kindergarten children made significantly more mistakes during retrieval than members of any of the other cohorts, and no significant differences were found among the rest of the cohorts. The results are summarized in Figure 7.

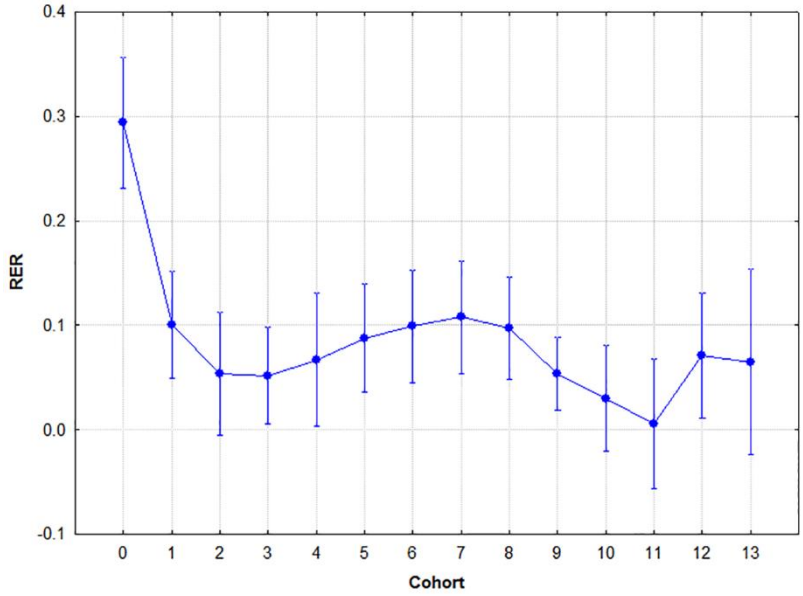

Figure 7.

Mean retrieval error ratios by cohort.
Circle: mean; whiskers: ±SD.

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). Thus no post-hoc analysis was conducted. The success of generalisation was fairly constant in the studied period. The results are summarized in Figure 8.

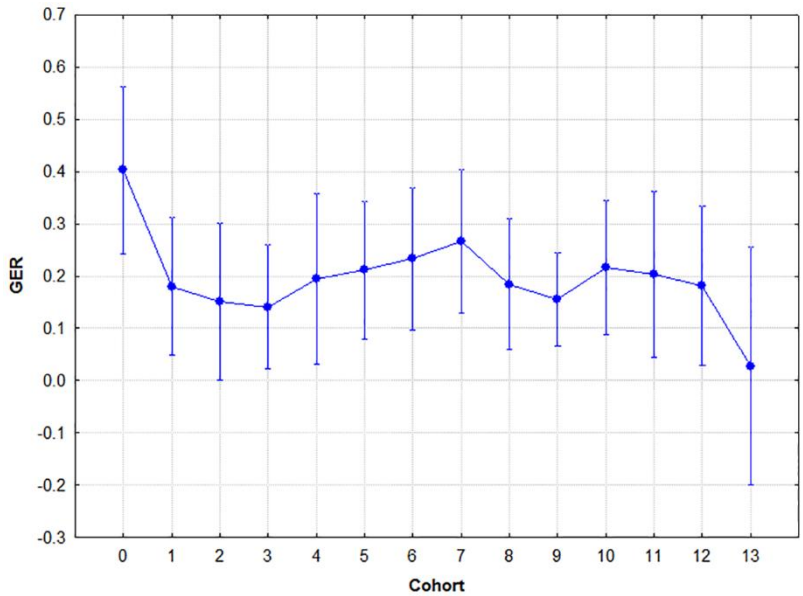

Figure 8.

Mean generalisation error ratios by cohort.
Circle: mean; whiskers: ±SD.

Additional analyses

We also wanted to know if the efficiency of acquisition (NAT, ALER) or the efficiency of retrieval (RER) had a significant effect on the success of generalisation (GER). 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.

A further way to characterise the efficiency of equivalence acquisition is to calculate the percentage of subjects in each cohort who failed to give correct responses altogether (no generalisation or erroneous rule abstraction) and who made no mistakes at all (stable generalisation) in the test phase. The high ratio of 100% correct responses in each cohort except for the youngest one is notable (mean: 44.21%). In contrast, 100% incorrect responses appeared only in a few cohorts, and at percentages below 10% (mean: 2.36%). A chi square analysis (100% correct responders vs. cohort) also supported the cohort-independence of generalisation performance (χ^2 =20.38, df=13, p= 0.1).

Finally, considering the high ratio of subjects who reached ceiling, we wished to make sure that it was not the ceiling effect that was reflected in the overall results. Additional ANOVA analyses were performed without the results of those who reached ceiling (for ALER, RER and GER). These analyses confirmed the original results: only cohort had a significant effect, and only in the case of ALER and RER (ALER p< 0.001; RER p< 0.05; GER p= 0.951) .

Study #2

All migraineurs and controls were able to complete both phases of the task. The results are summarised in Figure 9.

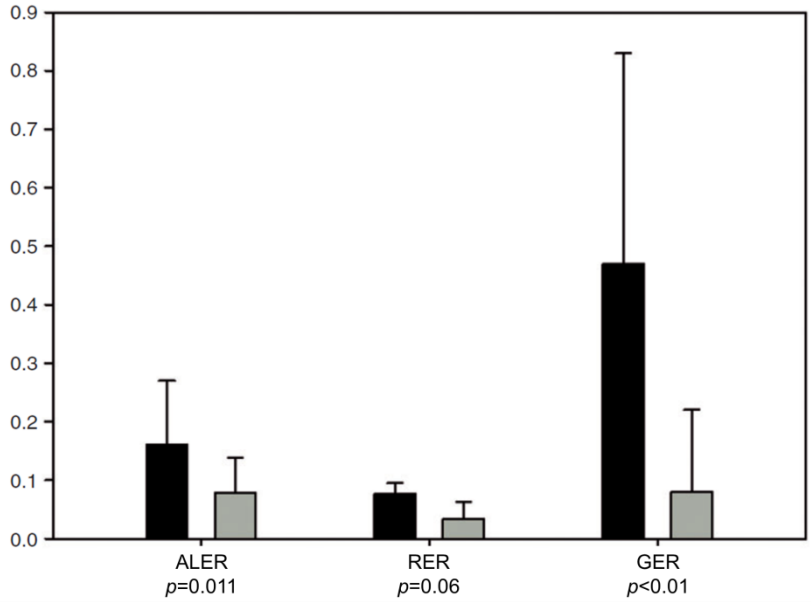

Figure 9.

Error ratios of migraineurs (black) and controls (grey). ALER: association phase error ratio; RER: retrieval error ratio; GER: generalization error ratio. Columns: means; error bars: SD

Number of acquisition trials (NAT) and association phase 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). This is also reflected in the fact that 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)

When tested for transfer, 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). The marked difference between the performances of the two groups during this phase is already apparent upon observing the distribution of subjects based on GER values. In the control group, 19 of the 22 participants (86.36%) stayed below an error ratio of 0.01. Twelve of these subjects (54.54% of the control sample) made no errors at all. The maximum error ratio in the control group was 0.5, reached by only one subject. In contrast, in the migraineur group, 14 subjects (63%) were characterized by error ratios over 0.5, including 4 subjects (18% of the migraineur sample) whose error ratio was 1.0. Only 5 subjects (22.7%) made no errors at all in this group.

Additional analyses

As the migraine group needed significantly more trials to reach criterion, they were overtrained. To check if this overtraining could have led to the significantly poorer performance of the migraineurs on the generalization part of the task, we conducted ANCOVA with the number of teaching trials as a covariate. Without the covariate ANCOVA returned almost exactly the same result as ANOVA (F=16.998, df=1, p<0.001). With the covariate the significance dropped, but the effect still remained highly significant (F=11.364, df=1, p=0.002). Interval therapy (flunarizine) had no effect on performance in any of the test stages (patients receiving interval therapy vs. patients not receiving interval therapy; p= 0.46, 0.98, 0.30; ALER, RER and GER respectively). According to the regression analyses, age did not have a significant influence on any of the test variables in either group (NAT: β=1.737, p=0.101; ALER: β=0.002, p=0.072; RER: β=0.001, p=0.516; GER: β=0.002, p=0.641), and in the migraine group, neither migraine duration in years (NAT: β=0.119, p=0.958; ALER: β=0.001, p=0.655; RER: β=1.711×10^{-5}, p=0.994; GER: β=0.013, p=0.068), nor attack frequency per month (NAT: β=4.637, p=0.231; ALER: β=0.003, p=0.449; RER: β=0.001, p=0.801; GER: β=-0.012, p=0.337), nor the estimated total number of attacks during the individual's lifetime (NAT: β=0.000, p=0.981; ALER: β=-6.317×10^{-7}, p=0.972; RER: β= 3.086×10^{-5}, p= 0.063; GER: β= 1.218×10^{-5}, p=0.849) made significant difference in any of the test variables. In other words, the test variables proved to be independent of these factors.

5. 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 cohort 0 (age 3-6) 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 cohorts 0 and 1 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 (2002, 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 (Myers et al. 2002, Myers et al. 2003). fMRI findings confirmed the latter, demonstrating that hippocampus indeed shows the highest activity among MTL structures during generalization task (Preston et al. 2004). Contribution of basal ganglia, specifically of the neostriatum, makes sense as well, as this task is partly an implicit category learning task (Urcuioli and Vasconcelos 2008), although a rather simple one. At the same time, the association phase undoubtedly involves an explicit component. For instance, the pairings can be described easily in a verbalized, declarative way (e.g. "the woman is paired with the blue fish"). Furthermore, there is evidence available of explicit system associated structures taking part to some extent in implicit memory. More specifically, several studies indicate MTL structures' involvement in neostriatum-linked learning (Turk-Browne et al. 2009, Simon et al. 2011, Shohamy and Turk-Browne 2013, Schapiro et al. 2014). The MTL has been found to govern responses in the early stages of category learning and also in other types of implicit learning. Then, over the course of training, the performance becomes increasingly dependent on the striatum (Kéri 2003, Schendan et al. 2003, Nomura et al. 2006, Simon et al. 2011). There is evidence to suggest that this reciprocal negative correlation might be mediated by the prefrontal cortex (Poldrack and Rodriguez 2004). Furthermore, the prefrontal cortex has been demonstrated to play an important role in category learning (Kéri 2003, Kincses et al. 2004).

On the other hand, as task complexity was found to correlate with the activity of the striatum in various tasks (Dagher et al. 1999, Lehéricy et al. 2005), the simplicity of the category learning component in RAET predicts a lower activity in this network.

Other important structures that are possibly involved in AE are the VTA and SN. The striatum-VTA/SN connection is a key component in feedback-driven learning (Delgado 2007). The activity of this connection is higher during the early stages of learning (i.e. the first few trials), then, as learning progresses, the reward-related response in the caudate nucleus diminishes. On the other hand, the VTA is connected to the hippocampi as well, and these structures show a gradual elevation in activity related to successful learning.

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 of Shohamy and Wagner (2008) the former procedure, associated with decreasing striatum activity is the dominant. VTA/SN activity increase, associated with reward-based learning was also observed (Shohamy and Wagner 2008). 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 (Shohamy and Wagner 2008), and the elevated activity during generalization (Preston et al. 2004). Therefore both phases rely on both systems, however functionally association performance is more basal ganglia-dependent, while generalization depends more on the hippocampi (Myers et al. 2002, Myers et al. 2003).

One possible explanation would be that although the basal ganglia are mature rather early in the structural sense (Clohessy et al. 2001, Lenroot et al. 2007, Knickmeyer et al. 2008), their functional development for this particular task is slower. This, however, is highly unlikely, as it contradicts findings on the development of other basal ganglia- related implicit learning forms. There is evidence available that infants as young as 4-months old can successfully cope with certain implicit learning tasks (Clohessy et al. 2001). This, of course, does not necessarily mean that other functions cannot show a slower pace of maturation. On the other hand, given the significant explicit component in this task and the fact that other implicit functions (e.g. sequence learning) are fully developed before the age of 3 (Diamond et al. 1994, Clohessy et al. 2001), it is less probable that the basal ganglia are the only structures that influence the acquisition of associations.

Considering these, we offer the following explanation of our results: our hypothesis proposes 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 of Ashby et al. (Ashby et al. 2011). COVIS 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 study of Huang-Pollock and colleagues (2011) supports this theory: the performance of children (8-12 years old) and young adults was compared in a category learning task, and the children were found to underperform adults. Based on their findings, the authors concluded that children performed more poorly because they were more likely to use an explicit strategy, and had greater difficulty in transitioning to an implicit approach. Minda and colleagues (2008) also demonstrated this effect.

A likely candidate for the component switching between memory systems is the prefrontal cortex. This structure is known to send extensive projections to both the hippocampi and basal ganglia, and was shown to be involved in their reciprocal activity (Poldrack and Rodriguez 2004). The prefrontal cortex matures long after the other two components (Gogtay et al. 2004, Sowell et al. 2004, Ofen et al. 2007), 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. As RAET was originally used for testing patients with various cognitive deficits (Myers et al. 2002, Myers et al. 2003, Bódi et al. 2009), it is indeed possible that the paradigm was too easy for our participants. This shows in the very low error ratios above kindergarten age. This, on the other hand, does not affect the validity of the results presented here: the factorial ANOVA performed without those who reached ceiling (i.e. 100% accuracy) showed that the ceiling effect did not interfere with the findings to a significant extent.

The lack of significant development in generalization might be explained more easily. The hippocampus shows the most marked structural maturation in the first two years of life (Giedd et al. 1996, Utsunomiya et al. 1999, Knickmeyer et al. 2008, Uematsu et al. 2012, Hu et al. 2013). Therefore, in the studied age range, the majority of hippocampal development is already over. The slow, gradual volume increase found until the age of 9-11 years does not show in our results. However, while no significant change of performance was found, a trend of higher GER could be seen in cohort 0. This can be interpreted as a possible sign of this system's ongoing development.

Another hypothesis to explain the high generalization performance of kindergarten children proposes that generalization depends on the hippocampus-VTA/SN-striatum rewarding network (Shohamy and Wagner 2008). 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 (this model is termed the integrative encoding mechanism), 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 (Gogtay et al. 2004)), the prefrontal cortex has been described to execute the higher control of this process (Tomita et al. 1999).

We did not observe age-related decline in performance. This is consistent with previous findings, that describe that the decline becomes apparent only in a higher age range (Rieckmann and Bäckman 2009, Rieckmann et al. 2010, Simon et al. 2011, Simon and Gluck 2013).

A common way to assess the explicit component of a task is testing if subjects were aware of a rule and consciously applied it (Reber and Squire 1998, Willingham and Goedert-Eschmann 1999, Song et al. 2007). We opted not to test for it, which might be seen as a weakness of the study, but we had reasons not to do so. First, criticisms have been made about verbal reporting to test for consciousness, as participants might be aware of features that are not addressed by the question (Shanks 2005). Second, especially young children must have had problems with grasping the very concept of consciousness. Third, as Shohamy and Wagner (2008)

suggested, generalization during AE can be seen as a type of false memory: participants might have a subjective sense of having already been exposed to pairings that, in fact, had never been encountered together. In terms of RAET: they might "remember" the unknown pairings, first encountered during the generalization phase, as if they have already seen them. The study of Meeter et al. (2009) also clearly demonstrated that the stimuli in RAET become equivalent through an alteration of their representation in the subjects' memory, so the two stimuli belong to the same category. Therefore once two stimuli are made equivalent it can affect the formation of episodic memories of them (Meeter et al. 2009). These points show that it would have been to little avail to test for awareness.

The effect of NAT, ALER and RER on GER

Nor NAT nor ALER had significant effect on GER. Therefore, performance during generalization phase did not depend directly on performance during association phase. On the other hand, significant correlation was found between ALER and RER: higher efficiency in learning stimulus pairs resulted in better retrieval. Our results also show that RER and GER had significant connection as well, that is, the better the participants were in retrieving the learned information, the better they could generalize. Therefore, acquisition does influence generalization after all, however only indirectly. The results demonstrate that the process of generalization is related more closely to retrieval than to acquisition, thus once enough information gathered for an efficient retrieval (regardless of how many trials are needed for this amount of information to accumulate), generalization will be highly efficient. This reflects in the lack of significant difference in the generalization performance of kindergarten children and older participants: even though these children needed more trials to acquire the associations, and they made more errors during retrieval too, they could generalize quite efficiently.

The effect of sex on the performance in RAET

No sex related difference was found in RAET performance, but it must be noted that the sexes were not completely equated across the cohorts (cohort 10,11 and 12 were dominated by female participants). However, the results demonstrate that sex does not influence the age-related development of RAET performance. The development of hippocampus was found to be sex dependent (Giedd et al. 1996), with girls achieving maximal volume later. This development during preadolescence probably causes subtle changes that our test could not detect.

The effect of migraine on the performance in RAET

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: once they managed to learn the stimulus pairs, they could retrieve them as effectively as healthy participants. On the other hand, 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 many 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 (Maleki et al. 2011, Maleki et al. 2013), our results can be interpreted as behavioural evidence of those structural changes. Maleki and colleagues (2011) described an initial increase of caudate volume in migraineurs (possibly due to adaptive structural plasticity), which is followed by a gradual decrease as migraine progresses. The caudate volumes of migraineurs with many attacks in their history are comparable with that of healthy subjects. 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. The structural changes of the hippocampi take place along a similar trajectory: an initial increase in volume, followed by a return to normal level (Maleki et al. 2013). Once again, our results show functional dysfunction, likely reflecting the structural alterations. These results are in line with that of

Myers and co-workers, who found a similar pattern of decrease in generalization performance in patients with hippocampal atrophy (Myers et al. 2002, Myers et al. 2003).

An alternative explanation to the lower generalization performance could be that it is only a secondary deficit that follows from the impaired acquisition performance. While this cannot be excluded based on experiment 2, the results of experiment 1 demonstrate that generalization performance is more linked to retrieval performance than to association phase: enough information for a successful recall was enough for a highly efficient generalization to happen among healthy conditions. The fact that retrieval was found to be unaffected by migraine makes this explanation quite unlikely.

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 (Gao et al. 2016). 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 (Myers et al. 2003) and long-term cocaine use (Vadhan et al. 2008). In Parkinson's, the availability of fronto-striatal dopamine is decreased (Lotharius and Brundin 2002), while in long-term cocaine users the D2-receptor availability in the striatum is limited (Martinez et al. 2004). Patients suffering from these conditions are characterized by decreased acquisition performance. While no significant SN alteration was found in episodic migraine (Welch et al. 2001), VTA activation was found in the premonitory phase of nitroglycerine induced migraine attacks (Maniyar et al. 2013), therefore the involvement of these structures in the decreased learning functions in migraine is possible. However, data available on this subject are insufficient for a conclusion.

We found no sex-related differences. However, the uneven distribution of sexes among the subjects does not allow a strong conclusion in this issue. This distribution is the consequence of the rigorous application of the diagnostic criteria, and the higher prevalence of migraine among women.

6. Conclusion

This study sought to examine how different factors affect AE performance. 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, the core element of any acquired equivalence task (and of several more complex cognitive functions), 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.

7. Summary

Acquired equivalence (AE) is a form of feedback-based associative learning where two or more stimuli are mapped to the same outcomes or responses. The performance on this task has previously been demonstrated to strongly depend on the functions of basal ganglia and the hippocampi. These structures and related functions have a distinct developmental trajectory: basal ganglia associated implicit memory functions mature early, while hippocampus-linked explicit memory functions show development late into adolescence. While several studies examined how various neurological and psychiatric conditions influence AE performance, studies dealing with the development of this function are scarce, and no study made an attempt to plot the development of this form of learning from early childhood to adulthood so far. Furthermore the basal ganglia and hippocampus are known to be affected in migraine, however there is no information available whether these alterations, described with imaging techniques also manifest on a functional level.

Therefore we assessed 265 healthy subjects aged 3 to 52 with the modified and Hungarian form of the computer based Rutger Acquired Equivalence Test (RAET), to examine the healthy development of AE performance (Study #1). The same test was used to measure the learning performance of 22 patients with migraine without aura, and an age- and sex-matched control group, to assess if migraine affects performance on this task (Study #2). RAET assesses three main aspects of AE: the efficiency of pair learning, the efficiency of the retrieval of acquired pairs, and the ability to generalise previous knowledge to a new stimulus.

In study #1 both pair learning and retrieval were found to exhibit development, with kindergarten children having significantly higher ($p<0.05$) error ratios than older participants. However these functions seem to reach adult-like level by the age of six. On the other hand generalization performance was found to be independent of age and sex on the examined age-spectrum. We propose that these results can be explained can be explained by either the earlier maturation of the hippocampi or the integrative encoding hypothesis, according to which generalization performance depends on faster maturing parallel dopaminergic midbrain-striatum/midbrain-hippocampus connections.

In study #2 migraine patients were found to show significantly poorer ($p<0.05$) performance in pair learning and generalization, with the deficit of the latter function being especially marked. In contrast, retrieval performance was on par with that of the healthy controls. Our

results support that basal ganglia and hippocampi (or at least their functional network) are involved in migraine without aura, and demonstrate that their structural impairments affect the associated learning functions.

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