Visual associative learning abilities of children with obsessive-compulsive disorder or Tourette syndrome

PhD Thesis

Ákos Pertich, MD

Supervisor: Dr. habil. Attila Nagy

Department of Physiology, Albert Szent-Györgyi Medical School
University of Szeged, Szeged

Doctoral School of Theoretical Medicine

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LIST OF PUBLICATIONS CONNECTED TO THE THESIS

I. **ÁKOS PERTICH**, GABRIELLA EÖRDEGH, LAURA NÉMETH, ORSOLYA HEGEDÜS, DOROTTYA ÖRI, ANDRÁS PUSZTA, PÉTER NAGY, SZABOLCS KÉRI AND ATTILA NAGY Maintained Visual-, Auditory-, and Multisensory-Guided Associative Learning Functions in Children With Obsessive–Compulsive Disorder ***FRONT. PSYCHIAT.***, 11:571053 (2020)
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II. GABRIELLA EÖRDEGH, **ÁKOS PERTICH**, ZSANETT TÁRNOK , PÉTER NAGY, BALÁZS BODOSI , ZSÓFIA GIRICZ , ORSOLYA HEGEDŰS, DÓRA MERKL, DIÁNA NYUJTÓ, SZABINA OLÁH, ATTILA ŐZE, RÉKA VIDOMUSZ, ATTILA NAGY Impairment of visually guided associative learning in children with Tourette syndrome. ***PLOS ONE***, 15:e0234724. (2020)
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I. GABRIELLA EÖRDEGH; ATTILA ŐZE, BALÁZS BODOSI, ANDRÁS PUSZTA, ÁKOS PERTICH, ANETT ROSU, GYÖRGY GODÓ, ATTILA NAGY Multisensory guided associative learning in healthy humans. ***PLOS ONE,*** 14:e0213094. (2019)
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IV. ANDRÁS PUSZTA, ÁKOS PERTICH, ZSÓFIA GIRICZ, DIÁNA NYUJTÓ, BALÁZS BODOSI, GABRIELLA EÖRDEGH, ATTILA NAGY Predicting Stimulus Modality and Working Memory Load During Visual- and Audiovisual-Acquired Equivalence Learning ***FRONT. HUM. NEUROSCI***., 14:569142 (2020)
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I. ÁKOS PERTICH, GABRIELLA EÖRDEGH, ANDRÁS PUSZTA ZSÓFIA GIRICZ, DIÁNA NYUJTÓ, ZSANETT TÁRNOK, PÉTER NAGY, ATTILA ŐZE, ATTILA NAGY Vizuálisan irányított asszociációs tanulás vizsgálata Tourette-szindrómás gyermekeknél 21. Látás Szimpózium, Pécs, 2019. június 21. (előadás)

II. ZSÓFIA GIRICZ, MÁRTON EDELMAYER, ÁKOS PERTICH, BALÁZS BODOSI, VIKTÓRIA BALIKÓ, DIÁNA NYUJTÓ, ÁGNES FEHÉR, GABRIELLA EÖRDEGH, GÁBOR BRAUNITZER, ATTILA NAGY Visually guided acquired equivalence learning and related memory processes in childhood migraine. IBRO Workshop, Szeged, 2020. 01. 29-30 P52

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LIST OF ABBREVIATIONS

ADHD	Attention Deficit and Hyperactivity Disorder
AE	Acquired Equivalence
AET	Acquired Equivalence Test
ALER	Acquisition Learning Error Ratio
ASD	Autism Spectrum Disorder
BG	Basal Ganglia
CA	Cornu Ammonis
CN	Caudate Nucleus
CRT	Cathode Ray Tube
DSM-V	Diagnostic and Statistic Manual of Mental Disorders, 5th Edition
GER	Generalization Error Ratio
GPe	Globus Pallidus, pars externa
GPi	Globus Pallidus, pars interna
MTL	Medial Temporal Lobe
MRI	Magnetic Resonance Imaging
NAT	Number of Acquisition Trials
OCD	Obsessive Compulsive Disorder
RAET	Rutger's Acquired Equivalence Test
RER	Retrieval Error Ratio
SN	Substantia Nigra
SNc	Substantia Nigra pars compacta
SNr	Substantia Nigra pars reticulata
SNRI	Serotonin and Norepinephrine Reuptake Inhibitor
SSRI	Selective Serotonin Reuptake Inhibitor
STN	Subthalamic Nucleus
TS	Tourette's Syndrome
TTS	Total Tic Score
YGTSS	Yale Global Tic Severity Scale

INTRODUCTION

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 humans and animals (1). Whether consciously or unconsciously, all of us use them in most of our activities during everyday life. These functions provide a considerable evolutionary advantage as they contribute significantly to our ability to adapt to our environment.

Learning refers to a change in behaviour that is the result of knowledge acquisition. It can be divided into subcategories based on the input modality (e.g., somatosensory, auditory, visual, etc.). Memory is the sum of processes that contribute to the encoding, consolidation and retrieval of knowledge (1). The two phenomena are hard to separate in definition, let alone on the functional level. Earlier investigations (2) concluded that implicit learning and implicit memory are not independent and argued that the same process might be underlying the performance in these tasks. Furthermore, it seems that the same structures are playing key roles in both functions (3–5). Learning is the process which makes the forming of memories possible, so it is analogous to the encoding process, at least to some extent. Moreover, we examine memory when we want to assess the efficiency of learning, our view on the success of learning is mostly dependant on the consolidation and retrieval processes. Considering these, we think of learning as a part of memory, thus in the following sections, *memory* refers to the whole system (including learning), and *learning* stands for the process of acquiring knowledge.

The classification of memory

In the model proposed by Atkinson and Shriffin in 1968, memory can be divided into three different, yet connected systems: the sensory register, the short-term store and the long-term store. The sensory register stores the sensory information incoming from various sources and inputs only for a brief time (generally considered to be in the range of 1 second), after which the information decays. Short-term memory (also known as working memory) is the system interposed between the long-term store and the sensory register, so it receives input from both, and its functions are holding and manipulating information. The information held here also

decays completely, though it takes a longer time (the timeframe is around 30 seconds) (6). This modular model had been challenged and been replaced by a more complex one. A new element, a so called central executive system was introduced, which is connected to passive storages (where information is registered until fading or getting displaced) and active storages (which allow the manipulation of information, like updating or refreshing 7). The elements of this system are scattered across the neocortex, however the prefrontal cortex, namely the ventrolateral and dorsolateral prefrontal cortices have a distinguished role in it (8).

Lastly, long-term memory is a mostly permanent repository in which knowledge of a former state of mind is stored even after the information in question had been out of conscious awareness for a longer period of time (1). The information stored here arrives from the short-term store. Long-term memory can be divided into two systems based on the aspect of conscious recollection: explicit and implicit memory (9).

Explicit memory

Explicit (also known as declarative) memory is a system that allows the conscious recollection of previously stored information (1). It can be further divided into two subdivisions: episodic and semantic memory, which are subsystems for personal experiences (i.e., memories concerning our lives, so called autobiographical memory,) and for facts (i.e., general knowledge about the world, like words and concepts), respectively (10). The explicit system is considered highly flexible, thus information stored here is accessible to multiple response systems, meaning multiple bits of information can be associated under different circumstances. It follows that changing the modality or surface characteristics of the stimuli has negligible effect on this type of memory (1,2,10). Learning occurring via this system is fast, however it is prone to forgetting and retrieval failure.

Explicit memory is noticeably homogenous in both structure and function. It is centred around the medial temporal lobe (MTL) its key structures are the hippocampal formation and the adjacent cortices (10–12).

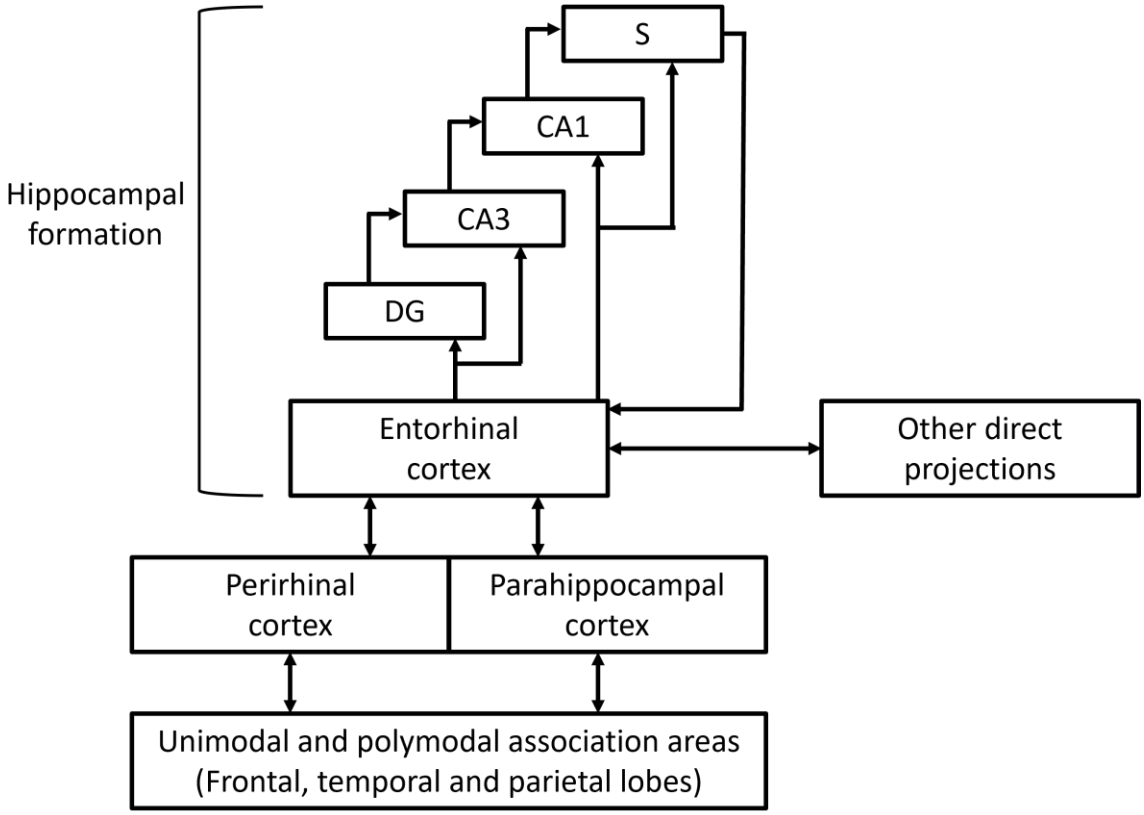

Figure 1.

Organization of the explicit system. DG: dentate gyrus; CA: cornu ammonis; S: subiculum Modified after Squire et al., 2004

Implicit memory

Implicit (also known as nondeclarative) memory is expressed through performance rather than conscious recollection, as the bits and pieces of knowledge acquired through this system are skills and procedures (such as riding a bicycle; 3,9,10,13,14). Because of this, the implicit system has been proposed as a kind of fine tuning of the perceptual-motor system through experience (15).

Nondeclarative memory differs from its declarative counterpart in several ways. Firstly, it is anatomically diffuse and covers a diverse functional range. Secondly, learning occurs gradually, relatively slower (priming being the single exception), however it is much more durable and reliable. Thirdly, it is much less flexible, thus information is not readily expressed by response systems that were not originally involved in the learning process (2,10). This translates to the system being sensitive to modifications of conditions: changes in surface

characteristics, modality or other alterations that require the application of the implicit knowledge among new circumstances result in significant decline of performance (16,17). Lastly, implicit memory has been described to be more robust and as such, it is less vulnerable to neurological insults (18).

Equivalence learning and RAET in general

Since the studies presented in the following sections are based on acquired equivalence learning, it is paramount that this specific type of learning is introduced in greater detail. Acquired equivalence (AE) is a learning paradigm that tests both explicit and implicit learning functions, as it is based on the formation of relationships between previously unrelated items. During this type of learning, generalization is induced between two superficially different stimuli (the so-called antecedents) that have been associated with similar outcomes (the consequents) previously. Less vaguely it means that participants learn that two (or more) stimuli are mapped onto the same responses or outcomes, thus they are equivalent in this respect (19). This kind of cognitive processing is found and described in humans (19–22). Myers et al. (20) have developed a learning paradigm to investigate a specific type of associative learning, visually guided equivalence learning, that is called Rutgers Acquired Equivalence Test (RAET), also known as the Fish and Face Test. In this test the participants have to buildacquire associations between antecedent stimuli (faces of cartoon characters) and consequent responses (drawings of fish of different colour) through trial and error. The test is divided into three different parts: acquisition (learning of face-fish pairs based on feedback), retrieval (recalling the previously learnt associations) and generalization (application of associations in previously unseen but deducible pairs), the last of which needs further elaboration. Unbeknownst to the participants, the associations follow a regularity. During the second part of the test, they have to apply this regularity for pairs that were not presented in the acquisition part (thus transferring or generalizing the regularity). Given the described details of the test, it follows that the acquired equivalence is functional in nature, as the stimuli are grouped according to their functional characteristics, rather than basic features (19). The above description is about visually guided associative equivalence learning and RAET in general. A more detailed description of the paradigm used in the presented studies is given in the Materials and Methods section.

Regions of the brain involved in the AET

Medial Temporal Lobe

A pivotal part of the long-term memory is the medial temporal lobe (MTL) which consists of the hippocampal and the anatomically related cortical areas: the parahippocampal, perirhinal and entorhinal cortices. The hippocampal formation can be further divided into the hippocampus proper (also known as Ammon's horn or cornu Ammonis) with its subregions, CA 1-4, the dentate gyrus and the subiculum (1,3,5,10). The hippocampal formation is well known as an essential structure of encoding and retrieval of explicit information and of spatial memory (23). This structure processes information from all sensory modalities, visual information included (5) hence it has been considered to play a key part in visual learning (3,5,10). The hippocampus is part of a hierarchically structured cortical processing network, where the hippocampus itself lies at the end of the hierarchy. The major source of its projections is the entorhinal cortex that provides both direct and indirect (through the CA3) input to CA1. Looking one step further down, the entorhinal cortex receives most of its cortical input from its adjacent regions, the perirhinal and parahippocampal cortices. The projections to these cortical parts originate in different associative areas (both uni- and polymodal) in the retrosplenial cortex, temporal, parietal and frontal lobes. The parahippocampal and perirhinal cortices play an outstanding role regarding the visual modality, as they receive input from unimodal and dorsal stream visual areas respectively (3,5,10).

Other structures associated with the declarative memory are the medial thalamus (24), the inferior temporal cortex (3) and the prefrontal cortex (25).

Basal Ganglia

The basal ganglia form a network of interconnected subcortical nuclei that include the caudate nucleus and the putamen (together forming the neostriatum), the external and internal parts of the globus pallidus (GPe and GPi), the pars reticulata (SNr) and pars compacta (SNc) of the substantia nigra (SN) and the subthalamic nucleus (STN). The basal ganglia exert their main functions primarily through cortico–basal ganglia–thalamo–cortical loops (26,27), however loops that originate subcortically have been identified as well (28). The body of the caudate nucleus and the STN serve as the main input structures of the basal ganglia, receiving direct

glutamatergic afferents from all around the cerebral cortex (29) as well as indirect projections from several subcortical areas, (e.g., inferior and superior colliculi, periaqueductal grey matter and other midbrain or hindbrain structures) through the thalamus (28). The main input areas of the basal ganglia then relay their signals, both directly and indirectly, to the principal output structures, that are the GPi and SNr. These nuclei, in turn project either directly to the thalamus, midbrain and medulla, or indirectly through the thalamus to cortical and limbic regions from which the original input to the whole network emerged (27,30).

Functionally, the basal ganglia form distinct circuits for different roles. However, they are organized parallelly, these loops should be viewed more as a continuum and less as subdivisions with very strict boundaries (30). Skeletomotor and oculomotor circuits play important roles in the focused selection of skeletal muscle actions and regulating saccadic eye movements, respectively (31). The dorsolateral prefrontal circuit connects the prefrontal cortex and the dorsolateral part of the CN directly. The lateral orbitofrontal circuit originates in auditory and visual association areas and projects to the ventromedial part of the CN. The anterior cingulate circuit connects limbic structures (entorhinal, perirhinal cortices, hippocampus and amygdala) with the ventral striatum. The last three circuits take part in various procedural learning functions (4,26,30). It was also described that the basal ganglia have important role in reward-driven mechanisms through the dopaminergic connections of the SN pars compacta-striatum and ventral tegmental area (VTA) – hippocampus pathways (32).

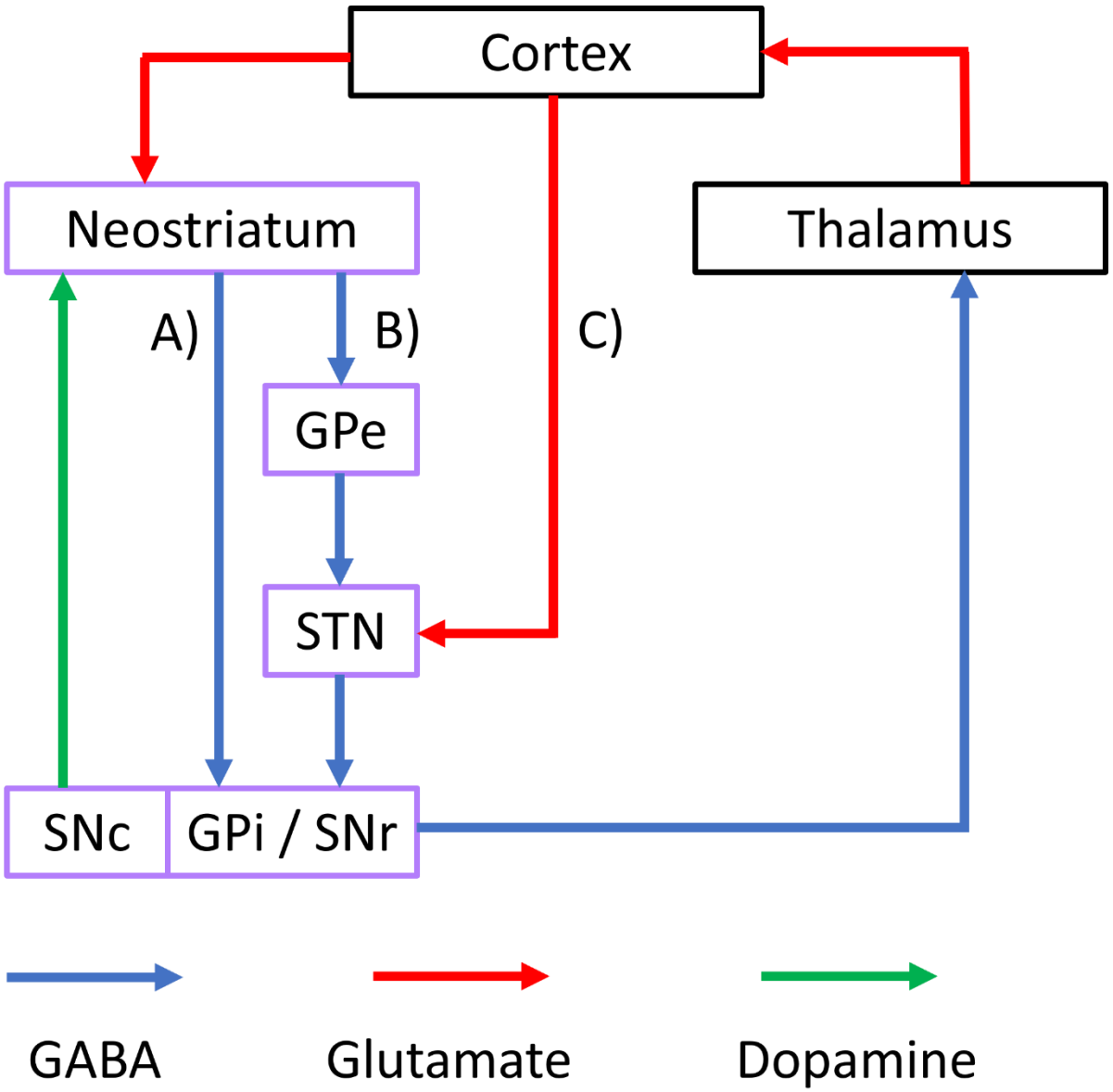

Figure 2. Structure of basal ganglia circuitry.

GPe, GPi: external and internal part of globus pallidus; SNc, SNr: substantia nigra pars compacta and reticularis; STN: subthalamic nucleus. Capital letters indicate the three main routes [A) Direct or "Go" pathway, B) Indirect or "non-Go" pathway, C) hyperdirect pathway] of the circuitry.

OCD and learning

OCD is affecting around 2-3% of both adult and child-adolescent populations, thus being one of the more prevalent human psychiatric disorders (33). It is possible for several different types of obsessions to form as a result of OCD, with compulsions emerging to counteract or mitigate these obsessions (34). Unfortunately, the exact pathogenesis of OCD is not fully understood yet, however we have knowledge of several alterations involved in OCD. Compared to healthy controls, different neurobiological abnormalities can be found, resulting in both morphological and functional changes. Structural and functional imaging of OCD patients has revealed higher cortical activation in the limbic and frontal associative cortices and the connected deep brain structures in the basal ganglia and hippocampi (35,36). Hence it seems that the cortico-basal ganglia-cortical loops are strongly involved in the pathogenesis of OCD (37). Several studies have addressed the question whether there is a change in cognitive function in OCD patients. However, concerning memory and learning functions, the results of these studies are far from being uniform. Both verbal and nonverbal memory functions had alterations in some of them but were not affected according to others (for a review see (38) in adults and (39) in children). However, to our knowledge, there was no information about the non-verbal learning of acquisition acquiring and the connected memory processes in pediatric OCD patients. Acquired equivalence learning (as described in greater detail earlier) is connected to the above-mentioned frontal cortex-basal ganglia loops and hippocampi but has not yet been investigated in children or adolescents with OCD. Since OCD is strongly connected to the dysfunction of the cortical-basal ganglia loops, our hypothesis was that the acquisition phase of the acquired equivalence learning test could be affected.

Tourette syndrome and learning

Tourette syndrome (TS) is a disorder presenting before the age of 18 years and affects 1% of school-aged children (34,40–42). The exact pathogenesis of TS is still unclear, however several underlying alterations are already known. The most frequent symptoms are motor and vocal tics (34,43), which significantly improve in many patients by young adulthood (44). In addition to the primary symptoms, pure Tourette syndrome is also associated with mild alterations in cognitive functions, mainly involving executive functions (such as verbal fluency, working memory and Stroop effect), which can extend into adulthood (45–47) and others,

which disappear with age (e.g. deficits demonstrated by the Wisconsin Card Scoring Test (48)). The symptoms of TS are mostly related to dysfunction of the basal ganglia and the connected frontal lobe areas (49,50). Beside the functional alterations, reduced left caudate nucleus volume (51), prefrontal hypertrophy and other structural changes (like a decrease in the volume of the gray matter in the anterior cingulate gyrus and right cingulate gyrus) were also described in TS (52–54). The connection between the frontal cortex and the basal ganglia via frontostriatal circuits (26,27,43,50,55–58) is significantly weaker in TS (4). This frontostriatal system is responsible for motor- and several cognitive functions (4). Descriptions of significant impairment in cognitive functions are rare in patients with pure TS (59) and the impairment often depends on the level of tic severity (60–62). Most deficits were reported in TS with its most frequent comorbidity, attention deficit hyperactivity disorder (ADHD, 63–65). Previous information shows that most alterations of cognitive functions are mainly present with concomitant TS and ADHD (20,66–69). These results suggest that the cognitive performance of patients with TS and ADHD is more similar to that of patients with ADHD than that of patients with TS only (20,67,70,71). In alignment with the previously cited articles, an investigation by Channon et al. did not find any impairment in memory (neither explicit nor implicit) or learning processes in TS alone but did find the above-mentioned impairments when TS and ADHD were both present (72). There are conflicting results in the field of reinforcement learning, but most of them show no difference between patients with TS and healthy controls (60,73–76). Although patients with TS have intact motor sequence learning (77) their procedural learning in a probabilistic classification learning, which is connected to the dorsal striatum (78) was significantly altered (79,80). However, hippocampus-related learning was not affected in patients with TS alone (80). Interestingly, implicit probabilistic sequence learning, which is another type of procedural learning was not affected or was even better in patients with TS (81,82). The mentioned learning functions are mediated via frontostriatal loops, as well as associative learning, which, to our current knowledge, has not yet been investigated for TS.

AIMS OF THE STUDY

The principal aim of the studies was to examine the visually guided associative learning functions connected to the basal ganglia and the hippocampus in children with OCD or TS. To this end, a simple, non-invasive psychophysical test was used to assess functions associated with these structures. It was also an intention to investigate whether any of these conditions cause any change in performance in these learning functions compared to matched, healthy controls.

Specific objectives of our studies were:

To examine the performance of children with OCD in visually guided associative learning and compare it to matched healthy controls

To examine the performance of children with TS in visually guided associative learning and compare it to matched healthy controls

To get information about altered basal ganglia and/or hippocampus functions in these patient groups.

To get information about the effect of medication on the learning performances of OCD and TS patients.

MATERIALS AND METHODS

Participants

There were three different groups of children participating in the investigations with a visually guided associative learning task: patients diagnosed with TS, OCD and healthy controls. Given that their demographic and descriptive statistical measures are different, the two patient groups are described separately with their respective controls in the following section. All participating children and their parents were informed about the background and goals of the study as well as the procedures involved. It was also emphasized that the participants were free to quit the study at any time (no one did so), and no compensation or benefit was given at the end of the tasks. Each participant and parent signed an informed consent form. The protocol of the study conformed to the tenets of the declaration of Helsinki in all respects, and it was approved by the Ministry of Human Capacities, Budapest, Hungary (11818-6/2017/EÜIG). All participating children were assessed with Isihara plates (83) prior to testing to exclude possible disorders of color vision. We estimated participants' IQ levels using the Standard and Colored Raven Progressive Matrices (84–86). The control groups were selected and matched from our larger database of children, recruited from local schools (Szeged, Csongrád-Csanád county, Hungary), free from any known psychiatric, neurological, neurodevelopmental or ophthalmic condition. All children in the patient and the control groups were white.

OCD patient group

During data collection, 43 pediatric OCD patients from the Vadaskert Child and Adolescent Hospital (Budapest, Hungary) were involved in the research. 12 of them had to be excluded from the further analysis because of the occurrence of several comorbidities beside the OCD. Four of them had ADHD, four had autism spectrum disorder, three had some kind of mood disorder, and one of them had epilepsy. The conducted study included 31 pediatric OCD patients without any comorbidity (n_{male} = 18), aged 7.5–17.5 (mean, 12.63 ± 2.72). All participants were white, free of ophthalmological, otological, neurological, or psychiatric conditions besides OCD. The diagnosis of OCD was made by both a licensed clinical psychologist and a board-certified child psychiatrist according to the Diagnostic and Statistical

Manual of Mental Disorders, 5th Edition (DSM-V) manual (34). To exclude disorders of color vision, the Isihara plate assessment was used prior to testing (83). Of the 31 children diagnosed with OCD, 16 were being treated with medications at the time of the tests (medicated group), while the other 15 were medication free during and before the investigation (unmedicated group). Fifteen children with OCD received selective serotonin reuptake inhibitors (SSRIs, such as fluvoxamine, sertraline, or escitalopram), and one got SSRI + SNRI (selective serotonin reuptake inhibitor and selective norepinephrine reuptake inhibitor: clomipramine). Three of the patients medicated with SSRI received other medications as well (clomipramine, benzodiazepine, or an atypical antipsychotic: risperidone).

From our database of healthy children, 31 control children (n_{male} = 18; mean age, 12.63 ± 2.73 years; range, 7.5–17.5 years) were assorted, who were matched one-to-one based on sex, age (differing in age by no more than 6 months), and IQ level to the patient group.

TS patient group

Altogether, 46 children with Tourette syndrome participated in the study. The children were recruited from Vadaskert Child Psychiatry Hospital in Budapest, Hungary. The children were diagnosed by both a licensed clinical psychologist and a board-certified child psychiatrist at the hospital according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-V) criteria (34). A total of 21 patients were diagnosed with Tourette syndrome without any other neurological or psychiatric comorbidities (TS group); 15 were diagnosed with Tourette syndrome and comorbid ADHD (TS + ADHD group); and 10 were diagnosed with Tourette syndrome and some other comorbidity (obsessive compulsive disorder [OCD] or autism spectrum disorder [ASD]; TS + OCD/ASD group). In this study, we analyzed associative learning abilities of 46 patients in the TS, TS + ADHD, and TS + OCD/ASD groups in detail (n_{male} = 32, mean age: 11.64 ± 2.38 years, age range: 8–17 years). The mean Yale Global Tic Severity Scale (YGTSS) total tic score (TTS) which is corresponding to the severity of the TS, was 20.7 ± 6.4 (range: 8–33) (Leckman JF, 1997; Kim S, 2019) in the whole patient group. Two participants showed minimal tic severity (TTS ≤ 10); 17 showed mild tic severity (score 11–20); and 19 showed moderate to severe tic severity (score > 20). There were no significant differences (Kruskal–Wallis ANOVA, $p > 0.05$) among the patient subgroups according to age, IQ level, and tic severity. Twelve of the children involved in this study (3 from the TS group, 6 from the TS + ADHD group, and 3 from the TS + OCD/ASD group)

were medicated because of the symptoms of their disorder(s). The TS group received dopamine 2 receptor antagonists (haloperidol and risperidone). The TS + ADHD patients received a norepinephrine–dopamine reuptake inhibitor (methylphenidate), a dopamine 2 receptor antagonist (haloperidol), or a partial agonist of the dopamine 2 and serotonin 1A receptors (aripiprazole), a norepinephrine transporter and dopamine reuptake inhibitor (atomoxetine), or melatonin. The TS + OCD/ASD group received selective serotonin reuptake inhibitors (fluvoxamine and sertraline), a partial agonist of the dopamine 2 and serotonin 1A receptors (aripiprazole), a serotonin and dopamine antagonist (risperidone), or a norepinephrine-dopamine reuptake inhibitor (methylphenidate).

From our database of control children, 46 children (n_{male} = 31, mean age: 11.55 ± 2.38 years, range: 8–17.5 years) were assorted and individually matched based on sex, age (differing in age by no more than six months), and IQ level to the patient groups. There were no significant differences (Kruskal–Wallis ANOVA, $p > 0.05$) among the control subgroups according to age and IQ level.

Visually guided associative learning paradigm

The tests were run on a personal computer, with the visual stimuli presented on a cathode-ray tube (CRT) screen. The tests were conducted in a quiet room with the children sitting at a standard distance (114 cm) from the screen. The M and X keys of the keyboard were labeled left and right, respectively. One child was tested at a time without a time limit so each participant could focus undividedly on the learning task. No forced quick responses were expected; however, the response times were measured during all phases of the test. A slightly modified and Hungarian translated version of the original Rutgers Acquired Equivalence Test (RAET, 20), rewritten in Assembly for Windows (originally written for iOS) was used with the written permission of Professor Catherine E. Myers (Rutgers University, NJ, USA), the corresponding author of the previously cited article. During the tests, the children had to learn to associate two independent pieces of information, referred to as the antecedent and the consequent. The participating children were expected to learn associations of antecedent and consequent stimuli through trial and error during the first half of the task and indicate their choice by pressing either the X (left) or M (right) button on the keyboard. The left or right button corresponded to a picture on the respective side of the screen when the visual stimuli were presented. The paradigm consisted of two different parts: the acquisition and the test

phases. During the first half, the acquisition phase, the child had to form associations between the presented stimuli (equivalence acquisition), and the program gave feedback about the success of the current trial (a green check mark if the answer was correct or a red X if not). After a given number of correct answers, new pairs were introduced one by one until six of the eight possible pairs had been presented. The children had to give a certain number of correct answers in a row after the presentation of each new pair before they were able to proceed to the next new pair or the second half of the test. The number of consecutive correct answers required was four after the presentation of the first two pairs, and the number increased by two after each new pair was introduced (thus, 12 correct answers in a row were required after all six pairs were introduced to progress to the second half of the test). This ensured that the children associated all the presented pairs and greatly diminished their chances of getting to the second phase based on pure luck. This naturally caused that the number of trials in the acquisition phase varied from participant to participant depending on their performance. The second, the test phase of the learning paradigm, where the program gave no more feedback about the correctness of the choices, can be further divided into two parts: retrieval and generalization. During the retrieval part, the child had to recall the pairs associated in the acquisition phase, while during the generalization part, two new hitherto unknown pairs were presented that were predictable based on the previously seen ones. The test phase had a fixed number (48) of trials, 12 of which included new associations, which were mixed among the already known ones from the retrieval phase.

During any given trial, the participant was shown a drawn face in the upper middle part of the screen with two colored fish below the face and was asked to choose a fish (Figure 3). The possible faces were all cartoon-like drawings of a boy, girl, woman, or man. The four fish were of identical size and shape, differing only in color: yellow, green, red, or blue. The four faces (A1, A2, B1, and B2) and the four different colored fish (X1, X2, Y1, and Y2) could create eight possible pairs during a single session of the task. These combinations were based on the antecedents (the faces). At the start of the task, the program randomly chose whether the faces of the same sex, same age, or same color of hair belonged together. At the beginning of the acquisition phase, the children had to learn that when face A1 or A2 was shown on the screen, it belonged with fish X1, not fish Y1 (green or yellow, respectively). The same applied to when face B1 or B2 was presented. The correct answer (fish) was Y1, not X1, the exact opposite of the previous scenario. This also meant that the children learned that faces A1 and A2 were equivalent in their consequents (belonged with the same fish, e.g., the yellow one) as faces B1

and B2 (belonged to the other fish, e.g., the green one). It clearly follows from the possible combinations that A1 and A2 could be the girl and the boy (same age), the girl and the woman (same sex), or the girl and the man (same hair color). Figure 4 shows only one possible iteration of the task. In the next stage of the acquisition phase, new consequents (red and blue fish) were introduced. If face A1 was shown, participants were expected to associate it with fish X2 (because the face was already associated with fish X1), not Y2, and in case of face B1, the correct answer was again the exact opposite (B1–Y2). When the aforementioned six pairs were presented and the participant gave 12 correct answers in a row, the test phase began. Up to this point, the children had received visual feedback in the form of a green check mark (correct answer) or red X (incorrect answer, Figure 3). During the test phase, no further feedback was given, and the program presented two new hitherto unknown combinations (faces A2 and B2 with the red and blue fish, X2 and Y2, respectively) mixed with the six already learned pairs. The participants had no knowledge of any possible new associations beforehand; however, if they learned that A1 and A2 were equivalent, similarly to B1 and B2, they could generalize from the previously learned associations and pair fish X2 with face A2 (the fish associated with A1) and fish Y2 with face B2 (the fish associated with face B1).

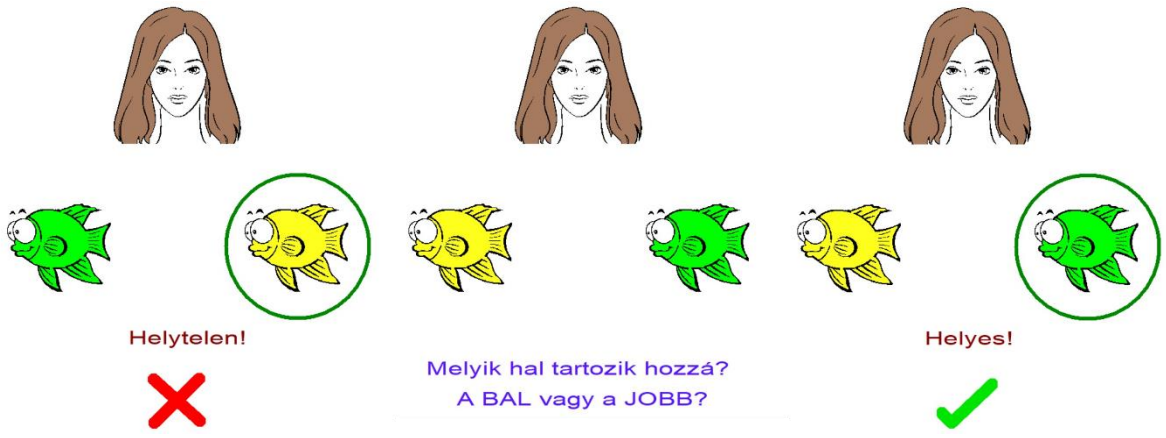

Figure 3. Example of a trial

Actual screen that the participants seen is in the middle, and potential feedback is depicted on the sides (left for wrong and right for right)

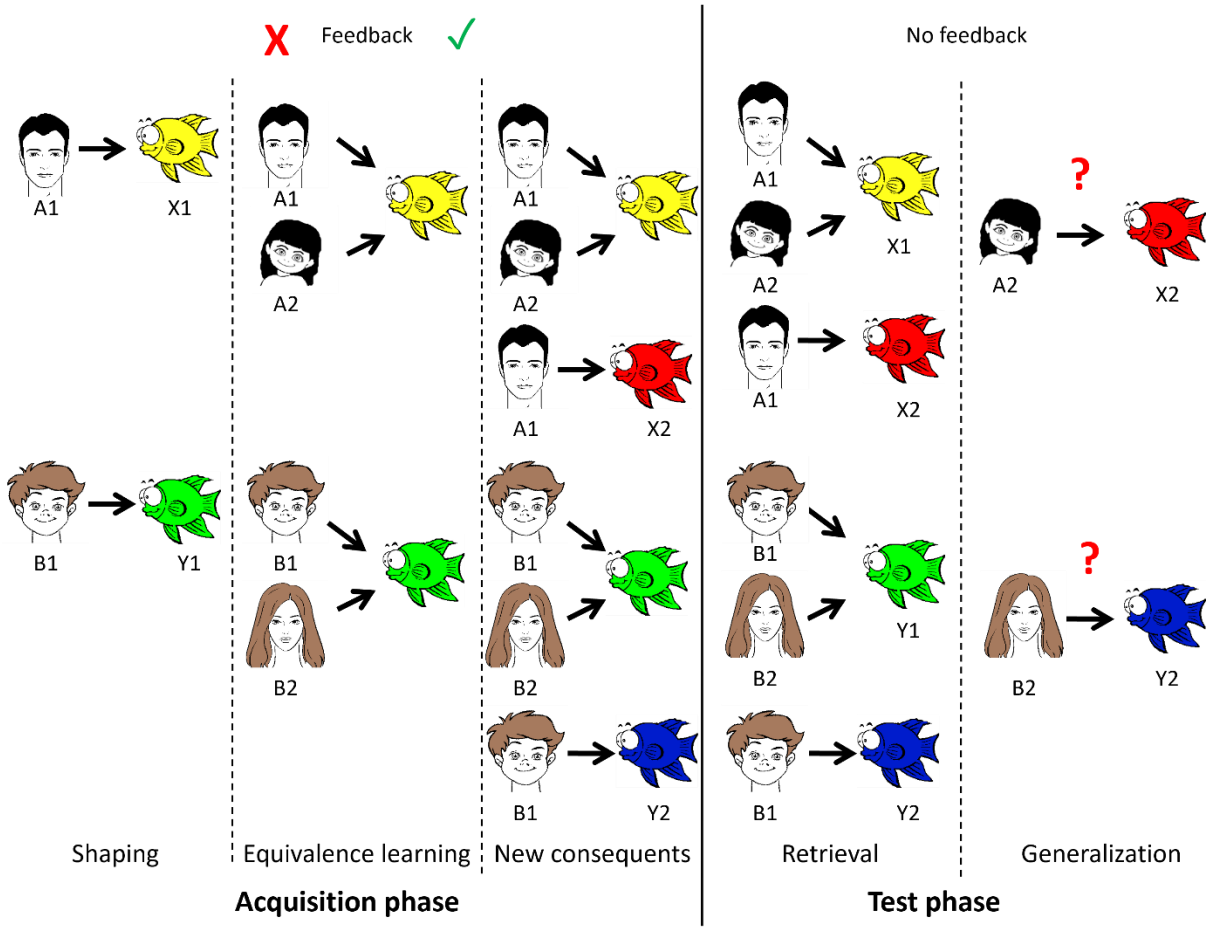

Figure 4. Schematic of paradigm

Example depicting the phases described in the text during a potential iteration of the visually guided learning paradigm. In the first phase (acquisition) participants learn the antecedent (faces) and consequent (fish) pairs through feedback. After learning 6 of the 8 possible pairs, they reach the second phase (test), where they do not receive feedback. Here they have to recall the previously learned 6 pairs, while being presented with the 2 pairs they have not seen before, but should be able to generalize, based on the deducted rule. In this iteration, people with the same colour of hair (man and girl, woman and boy) belong together.

Data analysis

The number of trials necessary to complete the acquisition phase (NAT: Number of Acquisition Trials), the number of correct and incorrect choices during the acquisition phase, and the number of correct and incorrect answers for known and unknown associations during the retrieval and generalization parts of the test phase were registered. From this data, error ratios were calculated: the ratio of correct answers to all answers in the acquisition phase (ALER: Acquisition Learning Error Ratio), in the retrieval part of the test phase (RER: Retrieval Error Ratio) and in the generalization part of the test phase (GER: Generalization Error Ratio). Response times (RTs) were measured in ms with ms accuracy for every answer in each phase. RTs exceeding the mean ± 3SD of the participants' response times were excluded from further analysis.

After testing for normality of data distribution using the Shapiro-Wilk normality test, comparisons between the performances of OCD or TS patients and their respective control groups were assessed using the Mann-Whitney U rank test or independent t-test. Median values and ranges or means and SDs are presented in the results section, respectively.

The statistical analysis was performed in TIBCO Statistica 13.4.0.14 (1984-2018 TIBCO Software Inc. USA) and CogStat 1.8.0 and 1.9.0 (2012-2020 Attila Krajcsi, 87).

RESULTS

The presentation of the results is divided into the comparisons between OCD patients and their control group and analyses concerning Tourette syndrome patients (and different subgroups of patients depending on the presence or absence of specific comorbidities) and their respective control groups.

Learning performances of OCD patients

Each pediatric OCD patient without any comorbidity finished the visual learning task, with only two of the patients being ineligible for the visual paradigm based on disabilities in color sight, as measured by the Ishihara plates (we let the children do the task so that they did not feel excluded but did not use their results). Thus, the data of 29 pediatric OCD patients with their matched healthy controls is presented.

Comparison of performances between OCD patients and their control group in Visually Guided Associative Learning Paradigm

We compared the performances, and none of the tested medians differed significantly from each other (Figure 5). The median of the NAT in the OCD group was 59.0 (range: 44–290, n = 29) and 67.0 (range: 42–139, n = 29) in the control group (Mann-Whitney rank test U = 402, p = 0.779). The median of the ALER was 0.0612 (range: 0.00–0.4103, n = 29) for the OCD group and 0.0725 (range: 0.00–0.2446, n = 29) for the control group (Mann-Whitney rank test U = 426, p = 0.938). The median of the RER was 0.0556 (range: 0.00–0.1667, n = 29) for the OCD group and 0.0556 (range: 0.00–0.25, n = 29) for the control group (Mann-Whitney rank test U = 404, p = 0.8). The median of the GER was 0.0833 (range: 0.00–0.6667, n = 29) for the OCD group and 0.0833 (range: 0.00–1.00, n = 29) for the control group (Mann-Whitney rank test U = 371, p = 0.431).

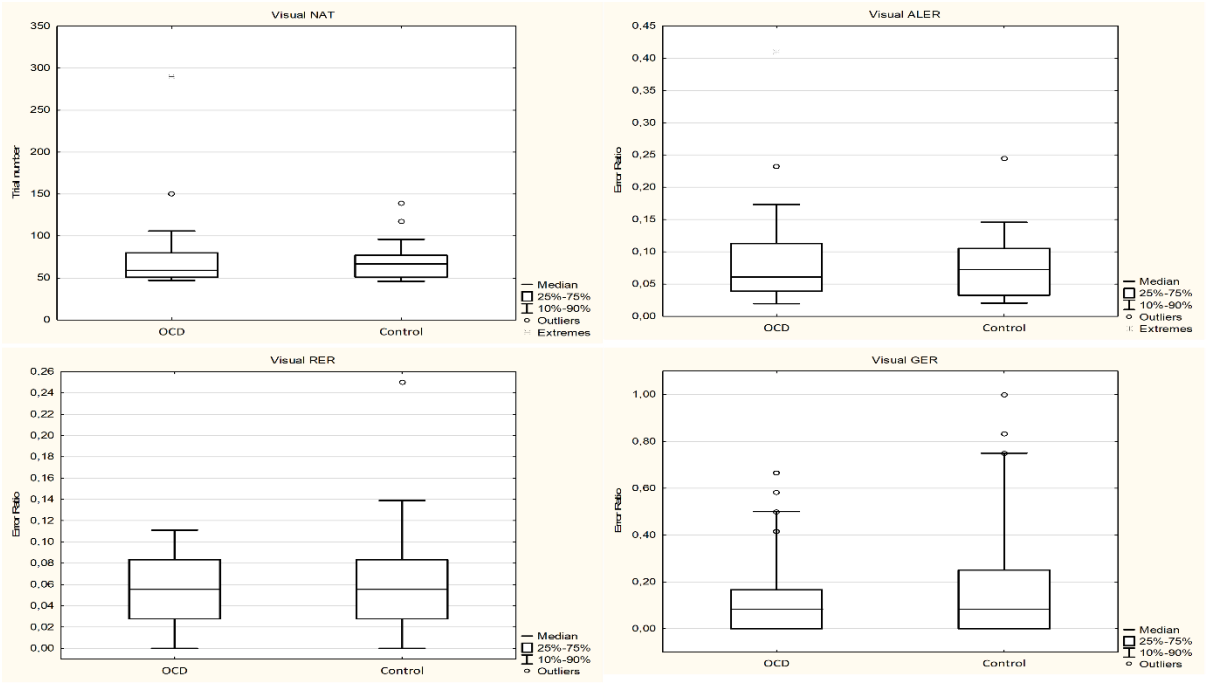

Figure 5. Performances of the obsessive–compulsive disorder (OCD) children in the visually guided equivalence learning paradigm.

NAT *shows the number of trials necessary to complete the acquisition phase of the paradigm.* ***ALER*** *shows the error ratios in the acquisition phase.* ***RER & GER*** *Show the error ratios in the two parts of the test phase: retrieval and generalization, respectively. In each panel, the first plot shows the performance of the patients, and the second plot shows the performance of the control children. The lower margin of the boxes represents the 25th percentile, the square within the boxes marks the median, and the upper margin of the boxes represents the 75th percentile. The whiskers encompass the 10 and 90 percentiles of the data. The points symbolize the outliers.*

The RTs were also not different between the OCD and the control groups in the entire learning paradigm. The median of RTs was in the acquisition phase174 ms (range: 968–4471 ms, n = 29) for the OCD group and 1590 ms (range: 1037–2455 ms, n = 29) for the control group (Mann-Whitney rank test U = 472, p = 0.428). During the retrieval part of the test phase, the median of the RTs was 1739 ms (range: 952–4425, n = 29) for the OCD group and 1786 ms (range: 1055–2697 ms, n = 29) for the control group (Mann-Whitney rank test U = 418, p = 0.975). In the generalization part, the median of the RTs was 2360 ms (range: 839–6630 ms, n = 29) for the OCD group and 2127 ms (range: 1103–4481 ms, n = 27) for the control group (Mann-Whitney rank test U = 351, p = 0.512).

The effect of medication on the performances of patients with OCD

Since we intended to investigate whether medication could have an effect on the performances, the performances of the two patient (medicated and unmedicated) and their matched healthy control subgroups were compared in a quadruple multiple comparison with Kruskal-Wallis ANOVA test. The results revealed no significant differences ($p > 0.05$) among the four subgroups in any of the investigated metrics (NAT, ALER, RER, and GER). Because of the absence of significant differences, we present the detailed pairwise comparison between medicated and unmedicated pediatric OCD patients only.

None of the tested parameters differed significantly between the two groups. The normality testing revealed normal distribution of the ALER and GER of the unmedicated groups and the RER of both groups. None of the tested parameters differed between the two groups in the visual task. The median of the NAT in the medicated group was 59.0 (range, 47–290; n = 15) and 59.0 (range, 44–102; n = 14) in the unmedicated group (Mann–Whitney rank test U = 123, p = 0.445). The median of the ALER was 0.0769 (range, 0.00–0.4103; n = 15) for the medicated group and 0.0609 (range, 0.0196–0.2323; n = 14) for the unmedicated group (Mann–Whitney rank test U = 96.5, p = 0.727). The median of the RER was 0.0556 (range, 0.00–0.1667; n = 15) for the medicated group and 0.0417 (range, 0.00–0.1389; n = 14) for the unmedicated group [independent samples t-test t(27) = 0.122, p = 0.904]. The median of the GER was 0.00 (range, 0.00–0.6667; n = 15) for the medicated group and 0.0833 (range, 0.00–0.5833; n = 14) for the unmedicated group (Mann–Whitney rank test U = 87, p = 0.425).

Learning performances of Tourette-syndrome patients

In the following sections, the performances of 46 pediatric patients with Tourette syndrome with and without comorbidities and 46 matched healthy control children are presented. All of the participants completed the entire visually guided acquired equivalence learning paradigm.

The performances of the entire TS group (with and without comorbidities) versus healthy control children

In order to reduce the effect of multiple (twice in this case) application of the same data, the statistical results were evaluated after Bonferroni correction at a significance level of 0.025. The median NAT was 79.0 (range: 42-202, n = 46) in all patients with Tourette syndrome (with and without medication) and 62.0 (range: 46-124, n =46) in the control group. The NAT values were significantly higher in patients with Tourette syndrome (Mann–Whitney rank test U = 636, $p < 0.001$). The median ALER was 0.102 (range: 0–0.325, n = 46) in all patients with Tourette syndrome and 0.085 (range: 0–0.186, n = 46) in the control group. The ALER values, similar to the NAT values, were significantly higher in patients with Tourette syndrome (Mann–Whitney rank test U = 690, $p = 0.004$). In the retrieval part of the test phase, there was no statistically significant difference (Mann–Whitney rank test U = 1.17e+0.3, $p = 0.360$) between the patients with Tourette syndrome (median: 0.056, range: 0–0.333, n = 46) and the control group (median: 0.083, range: 0–0.472, n = 46). In the generalization part of the test phase, similar to the retrieval part, there was no statistically significant difference (Mann–Whitney rank test U=1.26e+0.3, $p = 0.103$) between the patients with Tourette syndrome (median: 0.125, range: 0–0.667, n = 46) and the control group (median: 0.167, range: 0–0.917, n = 46, Figure 6).

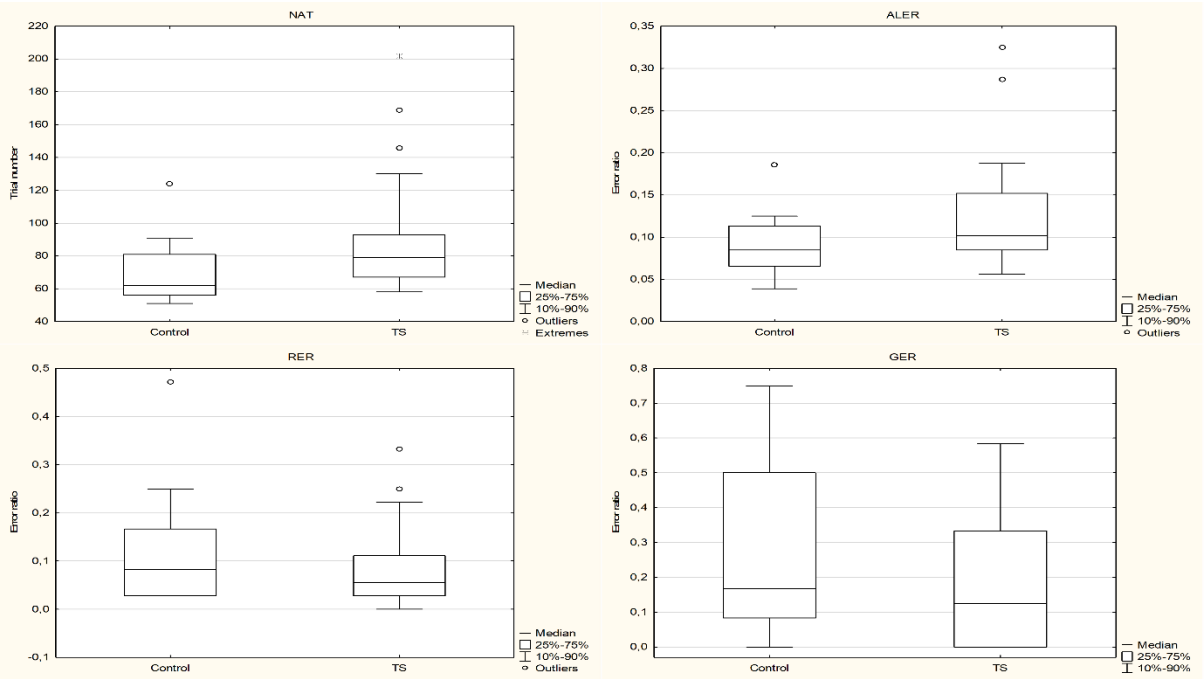

Figure 6. Performance of all patients with Tourette syndrome and healthy control children in the visually guided equivalence learning paradigm.

NAT denotes the number of the necessary trials in the acquisition phase of the paradigm. ALER shows the error ratios in the acquisition phase of the paradigm. Lower diagrams denote the error ratios in the retrieval (RER) and generalization (GER) parts of the test phase, respectively. In each panel, the first column shows the performance of all patients with Tourette syndrome, and the second column denotes the performance of the control group. The lower margin of the boxes shows the 25th percentile; the line within the boxes marks the median; and the upper margin of the boxes indicates the 75th percentile. The error bars (whiskers) above and below the boxes indicate the 90th and 10th percentiles, respectively. The dots over and under the whiskers show the extreme outliers.

The effect of medication on the performances of patients with Tourette syndrome with and without comorbidities

To examine the effects of medications on the performances in the applied visual associative learning paradigm, the performances of the unmedicated patients (TS, TS + ADHD, and TS + OCD/ASD) and their matched healthy controls, the unmedicated patients with Tourette syndrome and all patients with TS, and the medicated and unmedicated patients with Tourette syndrome were compared.

Unmedicated pediatric patients with Tourette syndrome versus healthy control children

As mentioned, to reduce the effect of multiple (twice in this case) application of the same data (first application is presented above in the comparison with the entire TS group), the statistical results were evaluated after Bonferroni correction at a significance level of 0.025. The median NAT was 78.5 (range: 42–202, n = 34) in all unmedicated patients and 60.5 (range: 46–124, n = 34) in the matched control group. The NAT values were significantly higher in patients with Tourette syndrome (Mann–Whitney rank test, U=345, p = 0.004). The median ALER was 0.102 (range: 0–0.325, n = 34) in patients with Tourette syndrome and 0.086 (range: 0–0.186, n = 34) in the control group. The ALER values, similar to NAT values, were significant higher in patients with Tourette syndrome (Mann–Whitney rank test U = 392, p = 0.023). In the retrieval part of the test phase, there was no statistically significant difference (Mann–Whitney rank test U = 657, p = 0.330) between the TS group (median: 0.056, range: 0–0.333) and the control group (median: 0.083, range: 0–0.472). In the generalization part of the test phase, there was no statistically significant difference (Mann–Whitney rank test U = 734, p = 0.053) between the patients with Tourette syndrome (median: 0.083, range: 0–0.667) and the control group (median: 0.208, range: 0–0.917, Figure 7)

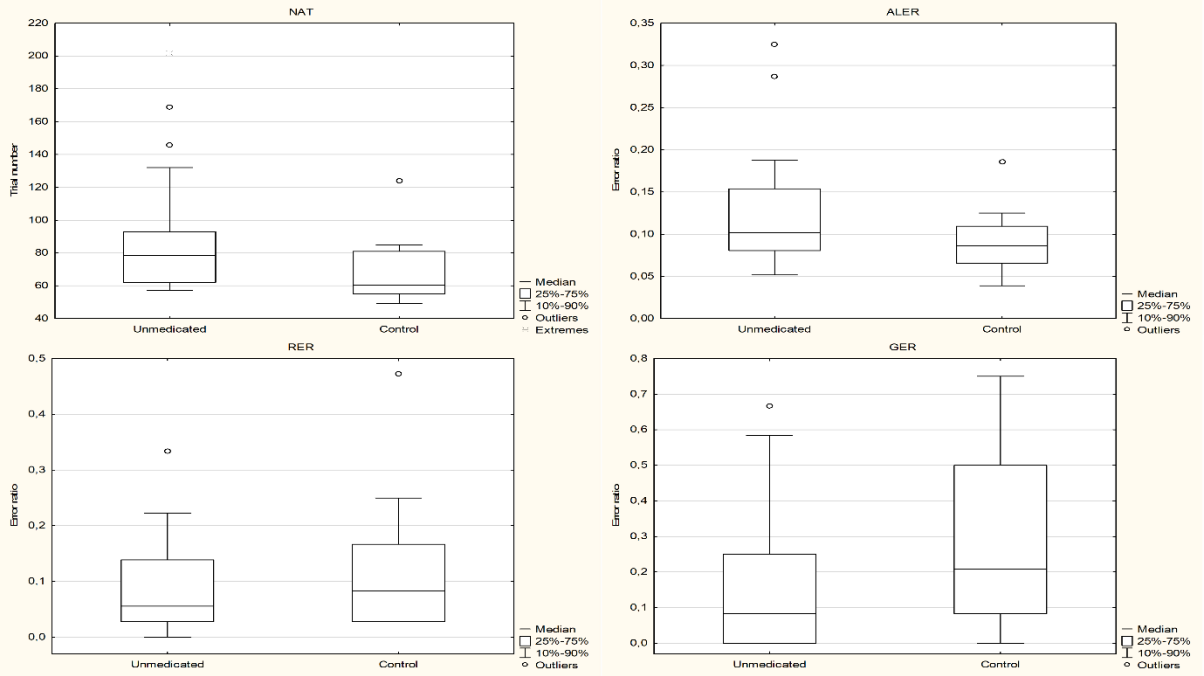

Figure 7. Performance of the unmedicated pediatric patients with Tourette syndrome versus that of healthy control children in the visually guided equivalence learning paradigm.

NAT denotes the number of the necessary trials in the acquisition phase of the paradigm. ALER shows the error ratios in the acquisition phase of the paradigm. Lower diagrams denote the error ratios in the retrieval (RER) and generalization (GER) parts of the test phase, respectively. In each panel, the first column shows the performance of all unmedicated patients with Tourette syndrome, and the second column (white) denotes the performance of the control group. The lower margin of the boxes shows the 25th percentile; the line within the boxes marks the median; and the upper margin of the boxes indicates the 75th percentile. The error bars (whiskers) above and below the boxes indicate the 90th and 10th percentiles, respectively. The dots over and under the whiskers show the extreme outliers.

All pediatric patients with Tourette syndrome versus unmedicated patients with Tourette syndrome

Comparing the performances of the whole patient group (TS, TS + ADHD, and TS + OCD/ASD) with the unmedicated patient group (TS, TS + ADHD, and TS + OCD/ASD), no significant differences were found. The median NAT was 79.0 (range: 42–202, n = 46) in the whole patient group and 78.5 (range: 42–202, n = 34) in the unmedicated patient group. There

was no significant difference in the NAT between these groups (Mann–Whitney rank test U = 763, p = 0.857). The median ALER was 0.102 (range: 0–0.325, n = 34) in the whole patient group and 0.102 (range: 0–0.325, n = 34) in the unmedicated patient group. The ALER values, similar to the NAT values, did not significantly differ (Mann–Whitney rank test U = 786, p = 0.969). In the retrieval part of the test phase, the median RER was 0.056 in the whole patient group (range: 0–0.333, n = 46) and 0.056 (range: 0–0.333, n = 34) in the unmedicated patient group, and this difference was not statistically significant (Mann–Whitney rank test U = 774, p = 0.937). In the generalization part of the test phase, the median GER was 0.125 in the whole patient group (range: 0–0.667, n = 46) and 0.083 (range: 0–0.667, n = 34) in the unmedicated patient group and this difference was not statistically significant (Mann–Whitney rank test U = 742, p = 0.698).

Medicated versus unmedicated pediatric patients with Tourette syndrome

The performance of the medicated patient group did not differ significantly from the performance of the unmedicated patient group. The median NAT was 79.0 (range: 68–101, n = 12) for the medicated patient group and 78.5 (range: 42-202, n = 34) for the unmedicated patient group. There was no statistically significant difference in the NAT between these groups (Mann–Whitney rank test U = 185, p = 0.643). The median ALER was 0.106 (range: 0.056–0.250, n = 12) in the medicated patient group and 0.102 (range: 0–0.325, n = 34) in the unmedicated patient group. The ALER values, similar to the NAT values, did not significantly differ (Mann–Whitney rank test U = 208, p = 0.920). In the retrieval part of the test phase, the median RER was 0.083 in the medicated patient group (range: 0–0.139, n = 12) and 0.056 (range: 0–0.333, n = 34) in the unmedicated patient group, and this difference was not statistically significant (Mann–Whitney U test U = 196, p = 0.840). In the generalization part of the test phase, the median GER was 0.208 in the medicated patient group (range: 0–0.667, n = 12) and 0.083 (range: 0–0.667, n = 34) in the unmedicated patient group, and the difference was not statistically significant (Mann–Whitney rank test U = 164, p = 0.319).

Comparison of the performances among the patients with TS, TS + ADHD, and TS + OCD/ASD

Firstly, the performances were compared in one multiple comparison of the three TS patient and the three control subgroups with Kruskal–Wallis ANOVA analysis. These results revealed significant differences among the six subgroups in NAT ($\chi 2$ (5, N = 92) = 14.1829, p = 0.0145) and ALER ($\chi 2$ (5, N= 92) =11.7513, p =0.0384) but not in RER ($\chi 2$ (5, N= 92) =1.9133, p =0.861) and GER ($\chi 2$ (5, N= 92) =3.3317, p =0.6490). After that the performances among the three TS patient subgroups were compared. There were no significant differences in the performances of the three patient groups (TS, TS + ADHD, and TS + OCD/ASD with or without medication) for any of the investigated parameters.

	TS (n= 21)	TS + ADHD (n= 15)	TS + OCD/ ASD (n= 10)	Kruskal- Wallis test
NAT	Median: 79 Range: 52 - 130	Median: 78 Range: 42 - 202	Median: 72 Range: 46 - 109	$\chi 2$ (2, N= 46) = 0.0498 P = 0.975
ALER	Median: 0.101 Range: 0.018 – 0.325	Median: 0.120 Range: 0 – 0.287	Median: 0.106 Range: 0.043 – 0.172	$\chi 2$ (2, N= 46) = 1.13 P = 0.568
RER	Median: 0.056 Range: 0 – 0.333	Median: 0.056 Range: 0.028 – 0.222	Median: 0.097 Range: 0.028 – 0.222	$\chi 2$ (2, N= 46) = 1.1 P = 0.577
GER	Median: 0.083 Range: 0 – 0.667	Median: 0.167 Range: 0 – 0.667	Median: 0.208 Range: 0 – 0.583	$\chi 2$ (2, N= 46) = 0.389 P = 0.823

Table 1. The performances of the Tourette syndrome, Tourette syndrome and attention deficit hyperactivity disorder, and Tourette syndrome and obsessive compulsive disorder or autism spectrum disorder groups (with or without medication)

After the subtraction of the performances of the medicated patients from the analysis, there were no significant differences among the TS, TS + ADHD, and TS + OCD/ASD groups

	TS (n= 18)	TS + ADHD (n= 9)	TS + OCD/ ASD (n= 7)	Kruskal- Wallis test
NAT	Median: 79.5 Range: 52 - 130	Median: 62 Range: 42 - 202	Median: 89 Range: 46 - 109	$\chi 2$ (2, N= 34) = 0.877 P = 0.645
ALER	Median: 0.102 Range: 0.018 – 0.325	Median: 0.097 Range: 0 – 0.287	Median: 0.136 Range: 0.043 – 0.172	$\chi 2$ (2, N= 34) = 0.694 P = 0.707
RER	Median: 0.056 Range: 0 – 0.333	Median: 0.056 Range: 0.028 – 0.222	Median: 0.028 Range: 0.028 – 0.222	$\chi 2$ (2, N= 34) = 0.535 P = 0.765
GER	Median: 0.083 Range: 0 – 0.667	Median: 0.083 Range: 0 – 0.161	Median: 0.167 Range: 0 – 0.583	$\chi 2$ (2, N= 34) = 0.255 P = 0.880

Table 2. The performances of the three unmedicated patient groups

DISCUSSION

The Rutgers Acquired Equivalence Test (also known as Face and Fish Test, 20), which investigates visually guided associative learning in humans, has a well-defined neurological background. The acquisition phase, which primarily depends on the function of the BG (20,88) tests the association between two different visual stimuli. The test phase, in which the previously learned associations (retrieval part) and new, but acquisition-based, predictable associations (generalization part) are evaluated, mainly depends on the hippocampi and the MTL (20,88). These cognitive functions were previously investigated in adult patients with different neurological or psychiatric disorders which were shown to be related to the dysfunction of the BG and the hippocampi (i.e., Parkinson's disease (20,68), Alzheimer's disease (89), and migraine without aura (90). However, to our knowledge, the previously presented two studies were the first to describe visual associative learning and alterations (or lack of them) in children with OCD or TS with or without comorbidities.

Effects of OCD on visually guided associative learning in children and adolescents

The remaining visually guided equivalence learning is an interesting finding because the majority of earlier studies showed that cognitive functions were altered in OCD patients (i.e., implicit sequence learning (91) spatial attention (92) and nonverbal memory (93) and only in rare cases did not find significant impairments in cognitive functions). Because of the strong involvement of the frontal cortex-basal ganglia loops in the pathogenesis of OCD, the hypothesis of the present study was that the first part of the paradigm, the acquisition phase, which mainly depends on the function of the basal ganglia, would primarily be affected. However, the OCD patients could build the associations with the same effectiveness as the healthy control children matched for sex, age, and IQ level. There are two possible explanations for this unaffected learning function. First, an explanation could be the compensatory function of the hippocampi of the basal ganglia dysfunction. This is in line with previous findings in which the hippocampi were able to compensate for the basal ganglia dysfunction in neurodevelopmental disorders (69,80). Moreover, MRI studies revealed that the volume

reduction of the hippocampi, which was observed in adult OCD patients, was not detectable in children with OCD (94). The second explanation is that OCD primarily affects the ventral (limbic) but does not affect or has a much weaker impact on dorsal corticostriatal loops (37,95). Similarly, to stimulus response or habit learning (4,78) acquired equivalence learning, which is primarily connected to the dorsal frontostriatal loops (4) was not significantly altered in children with OCD.

Similarly, to the remaining acquisition function, the retrieval and generalization parts of the test phase, which primarily depend upon the function of the hippocampus-MTL—a system that is less involved in the pathogenesis of OCD (94) than the BG-frontal cortex loops—were not altered either. Recent results have described some morphological changes in the hippocampi of adult OCD patients, but this has not yet been described in children and adolescents with the same disorder (96–98).

The question is raised as to whether the same performances in the psychophysical results were not due to the longer response times of the OCD patients. One argument could be that the longer response times of the OCD patients resulting from their compulsions could enhance their performances and decrease the number of bad decisions. However, similarly to the performances in the psychophysical tests, there were no differences between the response times of the OCD patients and the healthy control children. Thus, the participants with OCD took no more time to make decisions than the healthy controls.

In summary, the children suffering from OCD had the same performance as the controls in all phases of the applied visual associative learning paradigm. Thus, both the acquisition and the test phases, which are primarily connected to the function of the basal ganglia and the hippocampi, respectively, were not negatively affected by OCD. These findings support the neuroimaging and functional results that OCD affects the ventral (limbic) but not the dorsal corticostriatal loops (37). The results of our study support this as visual acquired equivalence learning, which is primarily connected to the dorsal frontostriatal loops, was not significantly affected in children with OCD.

Effects of TS on visually guided associative learning in children and adolescents

The alteration of visual associative learning in children with TS is an interesting finding because only in rare cases have significant impairments been described in any cognitive functions in TS. TS is strongly related to the dysfunction of the BG and the frontal associative cortex. Given the involvement of the BG in the pathogenesis of TS, the acquisition phase, which mainly depends on the basal ganglia, was primarily affected in the associative learning test. Based on our results, all patients with TS made the associations with less effectiveness than healthy control children. However, the retrieval and generalization parts of the test phase, which mainly depend on the function of the hippocampi, were not negatively affected by TS. Although the acquisition building was weaker, better performances (not statistically significant however) were found in the latter two parts of the paradigm, probably as a compensation of the hippocampus-MTL (69,80). Our results demonstrated that in the acquisition phase, the performance (NAT and ALER) of all patients (TS, TS + ADHD, and TS + OCD/ASD) was significantly weaker than in the sex, age, and IQ level-matched healthy control group. The question arises whether the alterations in equivalence learning in all patients with TS were primarily due to TS or its most common comorbidity, the ADHD. In most cases, TS and ADHD, which seems to play a major role, are jointly responsible for the alterations in cognitive functions (18,73,99,100). The performance of the three different patient groups were compared and no significant difference were found among them. This finding does not support the predominant role of ADHD in the described alterations in the acquisition phase of the associative learning task. The comparison of each patient group with its matched healthy control group revealed significantly increased NAT and/or ALER values in patients with TS without any comorbidities and TS + OCD/ASD but not in patients with TS + ADHD. These results together could suggest that concomitant ADHD was not primarily responsible for the visual acquisition learning deficits in patients with TS. This is in contrast with previous findings that ADHD is primarily responsible for the alteration of cognitive functions in patients with TS + ADHD (67,70,71,73). Therefore, the visually guided acquired equivalence learning, similar to stimulus-response or habit learning (4,78) which is mediated by the dorsal frontostriatal pathways, is more attributable to TS than ADHD, despite ADHD symptoms affecting the dorsolateral frontostriatal circuits (101). The volume of the hippocampi is significantly larger in patients with pure TS than that of their healthy counterparts (102), and no explicit memory (which is connected to the hippocampus) deficits were reported in children with TS (78,80).

Our results are in line with these findings. The performances in the retrieval and generalization parts of the test phase, which are primarily related to the hippocampi were not worse in the entire group of patients with TS with and without comorbidities. Concerning the three investigated subpopulations of the patients with TS (TS without comorbidities, TS + ADHD, and TS + OCD/ASD), the RER and GER values did not differ from those of the matched healthy control children.

Another question is the possible influence of medication on the performance of patients with Tourette syndrome with or without comorbidities. Because of the relatively low number of cases in the comorbid groups, we could not perform a valid comparison between the performance of medicated and unmedicated TS + ADHD and TS + OCD/ASD patients. Thus, we used the entire TS population (TS without comorbidities, TS + ADHD, and TS + OCD/ASD) to get information about the possible role of medication. The performances in the acquisition phase of the associative learning task in unmedicated TS pediatric patients, similar to the entire TS population, were significantly weaker than those of the matched healthy control children. The comparison of the performances of the entire and the unmedicated TS patient groups revealed no differences. Similarly, we found no differences between the performances of medicated and unmedicated pediatric patients with TS. These findings collectively suggest that medication had no or only a weak influence on our results.

In this study, we have functionally confirmed the results of neuroimaging (52–54,103) and functional studies that the dorsal frontostriatal circuits are strongly affected in TS, and these circuits are critical to the acquisition process of visually guided associative learning (79,80). The hippocampus mediated recall of previously learned associations, and the building of new but acquisition-based, predictable associations were not altered in TS.

CONCLUSION

In the previously described two studies, we managed to examine the performances in equivalence learning and connected memory processes of children with OCD or TS and compare them with those of age, sex and IQ matched groups of children without any neurological and psychiatric condition.

We found that children with OCD have no statistically significant difference in psychophysical learning performance and reaction time compared to those of their matched control group, in any part of the visual acquired equivalence learning paradigm. Furthermore, none of the tested parameters differed significantly between medicated and unmedicated OCD patients in the described visual associative learning paradigm. Thus, the medication influenced not the effectiveness of the associative learning abilities of the OCD patients. We argue that the unaffected visual acquired equivalence learning could be explained by the compensatory function of the hippocampi in BG dysfunction or the fact that acquired equivalence learning is much more dependent on the dorsal corticostriatal loops, which are not affected in OCD.

In contrast to the OCD patients, in the TS group, we found that pediatric patients have significantly poorer performances in the acquisition phase (NAT and ALER), but there are no differences in performances compared to those of their healthy controls in either part of the test phase. A possible explanation of the weaker performance in the acquisition phase in TS patients is that TS is primarily connected to the dorsal frontostriatal loop, in contrast to the role of the ventral frontostriatal loop in the pathogensis of OCD.

SUMMARY

Learning and memory are two basic functions of the nervous system, the latter of which can be classified into subgroups, based on several criteria, such as modality, longevity and the nature of the information stored. A specific type of learning is acquired equivalence learning, which is based on the formation of relationships between previously unrelated items. In the studies that form the backbone of this thesis, the visually guided equivalence learning was tested in pediatric OCD and TS patients, since the RAET has clearly established neural correlates, such as the MTL and the BG, and there is growing evidencein both states that these structures and corticostriatal loops are involved in their pathogenesis.

Three different groups of children (OCD, TS and a preconstructed database of healthy controls) were tested with a visually guided associative learning paradigm, the RAET, also known as the Face and Fish test. The test consists of two different phases, the acquisition, where new associations have to be learnt between faces and fish of different color, based on an unannounced, but deducible regularity, and the test part, where the previously formed associations have to be recalled. The latter phase can be further divided into two parts: retrieval, where the pairs associated in the previous phase have to be recalled, and generalization, where two, previously unknown but deducible pairs were shown. The number of trials needed to pass the acqusition phase (NAT), and the ratio of correct answers to all answers in all phases and parts (ALER, RER, GER) and reaction times were recorded in the patient groups and the matched controls and compared with the appropriate statistical tests (Mann-Whitney U test or t test fron independent samples).

A comparison of the performances of OCD patients and their control group revealed no difference in any recorded parameter (NAT, ALER, RER, GER, RT). The effect of medications on visually guided associative learning was also tested, but none of the parameters differed significantly between the medicated and unmedicated OCD patients either. Although, in the case of TS patients, there was a significant difference in performances during the acquisition phase (namely NAT and ALER) when compared to their control group. The same difference was still present when only unmedicated TS patients were compared to their controls, however no significant differences were found in performances between medicated and unmedicated TS patients, and the three subgroups of TS patients (pure TS, TS and ADHD, TS with OCD/ASD).

The unaffected visually guided equivalence in OCD is an interesting finding as the majority of earlier studies showed altered cognitive functions in OCD. A possible explanation for this could be that OCD affects the ventral but not the dorsal corticostriatal loops, the latter of which is primarily connected to visual acquired equivalence learning. On the other hand, the alteration of visual associative learning in TS is also interesting as significant impairments in any cognitive functions have rarely been described in TS. This functionally confirms the neuroimaging results that TS strongly affects the dorsal corticostriatal loops, which are crucial to the acquisition of visually guided associative learning.

In conclusion, our findings have shown that OCD does not impair visually guided associative learning, while TS does so, regardless of the presence of medications or comorbidities, possibly because the two states could affect different corticostriatal loops more (the ventral or the dorsal, respectively).

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