Sensory guided equivalence learning and its connection with borderline personality disorder

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Publications

I. Full publications published in a referred journal (List of publications connected to the thesis):

1. EÖRDEGH, GABRIELLA; ŐZE, ATTILA; BODOSI, BALÁZS; PUSZTA, ANDRÁS; PERTICH, ÁKOS; ROSU, ANETT et al. (2019) Multisensory guided associative learning in healthy humans. PLOS ONE 14 (3), e0213094.
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2. ROSU, ANETT; TÓT, KÁLMÁN; GODÓ, GYÖRGY; KÉRI, SZABOLCS; NAGY, ATTILA; EÖRDEGH, GABRIELLA (2022) Visually guided equivalence learning in borderline personality disorder. HELIYON 8 (10), e10823.
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II. Abstracts published in a referred journal:

1. ROSU, ANETT; EÖRDEGH, GABRIELLA; NAGY, ATTILA Human study of sensory directed associative equivalence learning. Hungarian Psychiatric Association XXI. Travelling rally, Siófok, Hungary, 2017. 01. 26-28. PSYCHIATRIA HUNGARICA (32) Suppl. I. 89 (2017)

III. Conference announcements:

1. ROSU, ANETT; EÖRDEGH, GABRIELLA; BODOSI, BALÁZS; ŐZE, ATTILA; NAGY, ATTILA Human study of multisensory directed associative equivalence learning. XIX. VISION SYMPOSIUM, Szeged, 2017. 02. 03. (lecture)

2. EÖRDEGH, GABRIELLA; ROSU, ANETT; GODÓ, GYÖRGY; NAGY, ATTILA Impairment of visually guided associative learning in patients with borderline personality disorder. IBRO WORKSHOP, Szeged, 2020. 01. 29-30 P51

List of abbreviations

ACC: Anterior cingulate cortex

AEL: Acquired equivalence learning

AL: Associative learning

ALER: Association phase learning error ratio

BG: Basal ganglia

BPD: Borderline personality disorder

CA: Ammon's horn

Cth: Cortical thickness

DG: Dentate gyrus

DLPFC: Dorsolateral prefrontal cortex

DSM-5:Diagnostic and Statistical Manual of Mental Disorders, fifth edition

FC: Functional connectivity

fMRI: Functional magnetic resonance imaging

GER: Generalization error ratio

GMV: Gray matter volume

GPe: External segment of globus pallidus

GPi: Internal segment of globus pallidus

HC: Healthy control

HPA: Hypothalamic-pituitary-adrenal

HPC: Hippocampi

ICD-10: International Statistical Classification of Diseases and Related Health Problems tenth revision

MTL: The medial temporal lobe

NAT: Number of acquisition trials

OCD: Obsessive-compulsive disorder

PCC: Posterior cingulate cortex

PTSD: Post-traumatic stress disorder

RAET: Rutgers acquired equivalence test

RER: Retrieval error ratio

S: Subiculum

SN: Substantia nigra

SNr: Substantia nigra pars reticulata

SNc: Substantia nigra pars compacta

STN: Subthalamic nucleus

VBM: Voxel-based morphometry

VTA: Ventral tegmental area

1. Introduction

1.1.1. Borderline Personality Disorder: definitions, classification, epidemiology, etymology

Borderline Personality Disorder (BPD) is characterized by emotion dysregulation, impulse control, intensive, unstable relationship and self-image (American Psychiatric Association, 2013, Chapman, 2019; Crowell & Kaufman, 2016). BPD or in other classification system (International Statistical Classification of Diseases and Related Health Problems tenth revision, ICD-10) the emotionally unstable personality disorder is a complex mental health disorder (World Health Organization, 2004; Stewart et al., 2019). BPD is classified in the Diagnostic and Statistical Manual of Mental Disorders fifth edition (DSM-5) under the dramatic cluster personality disorders. BPD often have comorbid other psychiatric disorders, such as affective, anxiety, post-traumatic stress disorder, substance use disorders, eating disorders, somatic symptoms disorder, dissociative, attention-deficit hyperactivity disorder and other personality disorder (American Psychiatric Association, 2013; Zanarini et al., 1998). In adolescence early diagnosis of BPD plays an important role in early intervention and effective treatment for BPD (Chanen et al., 2007; Guilé et al., 2018; Kaess et al., 2014). Earlier classification systems categorized all people with mental health problems into two groups, one of them the psychotics and the other neurotics. Then it was observed that a group of neurotics crosses the borderline of psychosis symptoms in a crisis situation (Moll, 2018). Based on this the concept the nomination "borderline personality disorder" was introduced in the 1960s.

By the DSM-5 patients have to meet at least five out of nine criteria to get to diagnose borderline personality disorder (American Psychiatric Association, 2013). In Europe ICD-10 is applied in the daily routine, where this disease is mentioned as emotionally unstable personality disorder (World Health Organization, 2004).

BPD is the most common personality disorder; its prevalence rate is 2%–3% in the adult population (Swartz et al., 1990). BPD incidence is significantly higher in women than in men (Battle, 2013).

Borderline personality disorder occurs in 20 percent of psychiatric hospitalized patients and can be estimated 10 percent of outpatients (Black et al., 2007). The genetics, neurobiological factors, environmental factors, childhood trauma and

congenital brain abnormalities could contribute to the development of the BPD (Gunderson et al., 1997). The heritability of BPD is approximately between 37% and 69% (Gunderson et al., 2011). Thus 37 to 69 percent of the occurrence of the BPD has genetical background. Torgersen and colleagues (2000) found that BPD was estimated to be the third most heritable personality disorder of all (Torgersen et al., 2000). Twin, sibling, and family studies have found that impulsive aggression is only partially heritable, but studies of serotonin-related genes have not indicated aggression behavior (Goodman et al., 2004).

One of the main factors involved in the development of the borderline personality disorder is childhood trauma or adverse childhood experience. Specific neurobiological factors were identified and dysregulations of the hypothalamic-pituitary-adrenal (HPA) axis and modified cortisol level were also found in BPD patients who have experienced childhood trauma.

Cortisol plays important role in the stress response, which is regulated by the hypothalamic-pituitary-adrenal axis (HPA axis). So, hyperactive HPA axis and elevated cortisol levels were found in these patients (Grossman et al., 1997). This is the reason for the greater stress response, which may be the reason for their higher vulnerability and irritability (Chapman & Gratz, 2007). Considering that the traumatic events can raise the cortisol level and the activity of HPA axis, the higher cortisol levels and the activity of HPA axis occurred more often in BPD patients with childhood traumatic events (Chapman & Gratz, 2007).

There is a close connection between the development of BPD and childhood abuse, especially child sexual abuse (Ball & Links, 2009; Cohen, 2008; Herman, 1992; Quadrio, 2005). Development of BPD symptoms was predicted not only childhood sexual abuse but the suppressed negative emotions and the intensity and reactivity of suppressed negative emotions could trigger the BPD, too (Rosenthal et al., 2005).

1.1.2. BPD symptoms (American Psychiatric Association, 2016)

1. Desperate effort to avoid real or imagined abandonment (note: criterion 5 suicidal or self-injurious behavior is not included).
2. A pattern of unstable and intense interpersonal relationships characterized by extreme alternation of idealization and disdain.
3. Identity disturbance: markedly and permanently unstable self-image or self-worth.

4. Impulsivity in at least two potentially self-harming or self-endangering areas (e.g., spending, sex, careless driving, binge drinking) (note: the 5 criteria for suicidal or self-injurious behavior does not belong here).
5. Repetitive suicidal behavior, gestures threats or self-injurious behavior.
6. Affective instability as a result of significant mood reactivity (e.g. intense episodic dysphoria, irritability or anxiety, which usually lasts for a few hours and rarely lasts more than a few days.
7. Chronic feeling of emptiness.
8. Inadequate, intense anger or anger control, difficulty (e.g. frequent outbursts of anger, constant anger, repeated fights).
9. Absent, stress-related paranoid thoughts or severe dissociative symptoms.

1.1.3. The effect of BPD on the brain: structural and functional differences

Several parts of the central nervous system (i.e. prefrontal cortex, caudate nucleus, limbic system, anterior cingulate cortex (ACC) and the brain areas of the HPA axis and other related structures) could be involved in the pathophysiology of the BPD (O'Neill & Frodl, 2012).

Anthony Ruocco and colleagues (2013) have pointed out two patterns of brain activity that may be the background of emotional dysregulation in BPD. One of it is the experience of increased emotional pain in line with the increased brain activity and the second is the decreased activity of brain circuits, which could suppress the increased emotional pain. However there were strong individual differences in the dysfunction of the limbic system (Ruocco et al., 2013). Several neuroimaging studies revealed in BPD patients the volume reduction of the brain regions involved in the regulation of emotion and stress responses, i.e. the hippocampus, the orbitofrontal cortex and the amygdala (O'Neill & Frodl, 2012). On the other hand, Ruocco and Schulze observed increased gray matter volume (GMV) in the hippocampus and amygdale than in healthy controls (Ruocco et al., 2013; Schulze et al., 2016). Aguilar-Ortiz (2018) also detected a significant reduction in GMV in the dorsolateral and medial frontal cortices, but the reduction was not found in the hippocampus and/or amygdala. Sampedro and colleagues (2021) reported decreased GMV in prefrontal cortex in BPD. Further, GMV reduction was found in the dorsolateral frontal cortex

and the medial frontal cortex, too. These cortical regions seem to be involved in cognitive control and the dysfunction of them could contribute to the development of BPD (Aguilar-Ortiz et al., 2018; Sampedro et al., 2021). Sampedro and colleagues (2021) found that the prefrontal cortex is thinner in BPD patients than the cortex of the healthy controls (Fig. 1.). This study supported previous results, which examined neuropsychological dysfunction and also found connection between reduced GMV in the ACC and enhanced impulsiveness (Soloff et al., 2003) and with general clinical severity (Aguilar-Ortiz et al., 2018; Sampedro et al., 2021). A PET study detected functional differences in orbitofrontal and ventromedial prefrontal cortex regions, which are involved in response inhibition, impulsivity regulation and reactive aggression (Blair, 2016; Soloff et al., 2008). Impulsivity and aggressive behavior were connected with frontal lobe hypometabolism (Salavert et al., 2011; Schulze et al., 2016) and decreased blood flow in the medial and orbitofrontal cortex (Wolf et al., 2012). McGarry and Carter (2017) observed that the prefrontal cortex is connected to the basolateral amygdala; the strongest inputs from the amygdala go back to the prefrontal cortex and to hippocampus but weaker inputs reach the striatum, too. These pathways are involved in emotional and motivated behaviors as fear and anxiety (McGarry & Carter, 2017). In BPD decreased GMV in prefrontal cortex and larger GMV in limbic system could partially interpreted these differences in emotional regulation and behavior response. This surprisingly intense activity may explain why fear, sadness, anger and shame can be very intense and long-lasting in BPD people (Chapman & Gratz, 2007). Yang and colleagues (2016) detected increased gray matter in regions including the bilateral supplementary motor area, dentate gyrus and bilateral precuneus, which reach to the bilateral posterior cingulate cortex (PCC). This may indicate reduced working memory, but improved episodic memory (Yang et al., 2016). The heterogeneity of neuroimaging results was interpreted partially by methodological differences, psychotropic medication and different age of the patients (Arens et al., 2013; Giuliani et al., 2005; Schulze et al., 2016).

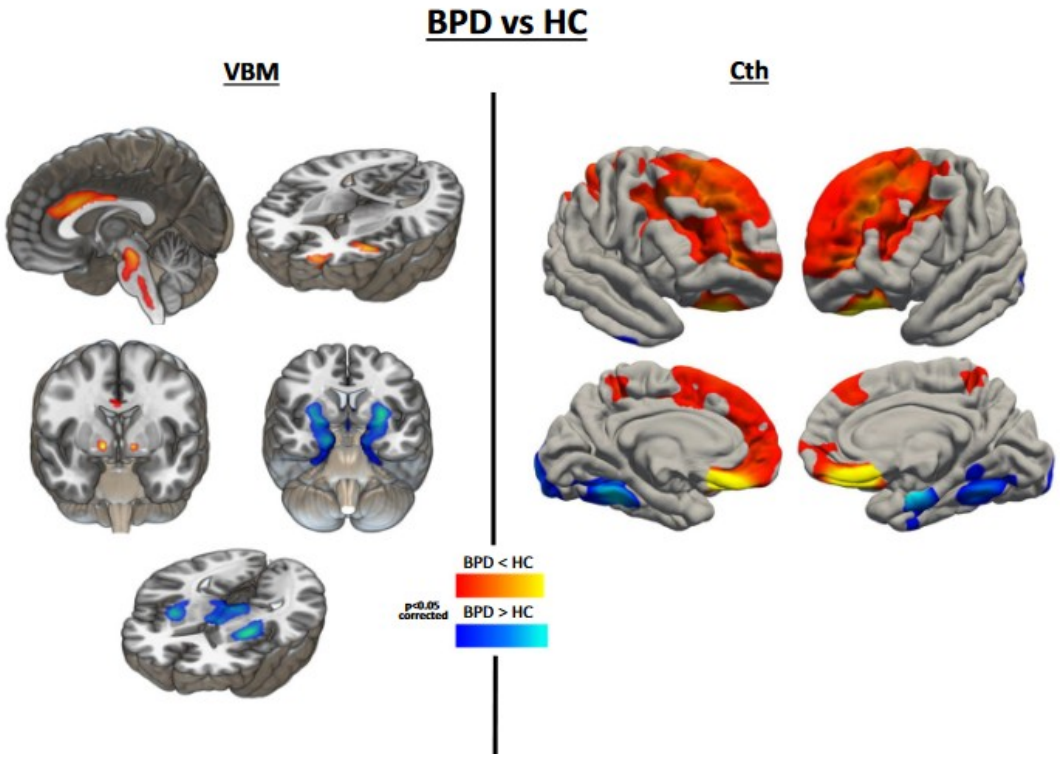

Fig.1.
Structural differences between BPD and healthy control (HC) groups in voxel-based morphometry (VBM) and cortical thickness (Cth)
From: Sampedro et al., 2021. Structural brain abnormalities in borderline personality disorder correlate with clinical severity and predict psychotherapy response

With the relative inactivity of the prefrontal cortex observed in BPD patients, we can understand the difficulties these patients in regulating their emotions and the stress response, given that the prefrontal cortex is involved in emotion regulation (Chapman & Gratz, 2007).

Da le Fuente and colleagues (1997) and Goyer and colleagues (1994) found relatively decreased glucose metabolism in the frontal cortex, limbic system, basal ganglia and the resting thalamus (De La Fuente et al., 1997; Goyer et al., 1994). In contrast, Juengling and colleagues (2003) detected hypermetabolism in the anterior cingulate cortex and in several parts of the frontal cortex. Hypometabolism was showed in the limbic structure of the left hippocampus, in the left cuneus and in occipital region included visual processing (Juengling et al., 2003).

Brambilla and colleagues (2004) examined volume deviations in the putamen, which is also part of the basal ganglia. The putamen has a role in strengthening learning, the abnormality, which is even more likely occurs among alcohol and drug abusers. With participation of 10 BPD patients with comorbid disorders (no

medication for two months) were found decreased hippocampal volume and increased putamen volume (Brambilla et al., 2004; Lis et al., 2007). The greatest impairment was detected in the area of decision-making, which indicated impairment of orbitofrontal cortex and the anterior cingulate cortex (Carrasco et al., 2012; Rüsch et al., 2010; Unoka & J Richman, 2016). The BPD symptoms of identity disturbances and dissociations may be elicited by the decrease volume of hippocampus (Ruocco et al., 2012) and the fronto-limbic dysregulation (Minzenberg et al., 2007; Salavert et al., 2011), which can influence the memory processes. In BPD patients visuospatial abilities may associate to parietal dysfunctions, too (Zago & Tzourio-Mazoyer, 2002). Slower cognitive processing speeds probably could indicate white matter damage, which limits communication and coordination in the central nervous system (Carrasco et al., 2012; Minzenberg et al., 2007; Turken et al., 2008; Unoka & J Richman, 2016).

The question was whether the putamen and caudate nucleus hyperactivation could be interpreted as a neural correlate of reduced emotion acceptance (Gratz & Tull, 2010). Decreased acceptance of emotions increase the need to respond to averseness. The striatum processes emotions and motion control in cooperation with the prefrontal and the limbic brain regions (Stathis et al., 2007). While the putamen is primarily responsible for the implementation of behavior, the activation of the caudate body plays an important role in the planning of goal-directed behavior (Balleine et al., 2007; Grahn et al., 2008). Especially, when a specific behavior is expected to have a positive outcome, the activation of the caudate nucleus is enhanced (Tricomi et al., 2004). D'Argembeau and colleagues (2008) observed increased activation in the caudate nucleus when BPD patients anticipated near-future events. This activation can be explained as mental simulation of upcoming emotional experiences and positive triggered actions (D'Argembeau et al., 2008). Therefore the striatal hyperactivation can be explained as a neural circuit of behavioral reaction to pressing and unaccepted emotional experience or cognitive execution processes (Li et al., 2013). In BPD the dorsostriatal (putamen and caudate) hyperactivation can be explained as neural correlate of a greater cognitive–executvie processes in response to an unacknowledged emotional experience. Hyperactivation was also found in the posterior part of the superior frontal gyrus and the precentral gyrus. In BPD patients the higher activation of the dorsolateral prefrontal cortex (DLPFC) could be a sign of increased executive control, which could affect false emotions and decrease in the acceptance (Lamers et al., 2019).

1.1.4. BPD and cognitive functions

Unoka and colleagues (2016) found several cognitive impairments in BPD patients. These impairments are highly heterogenous and it is important to calculate with the moderating effect of parents' education and comorbid diseases. The degree of cognitive impairment identifying was different. Large difference was found in the case of decision making, memory and executive functions. It was moderated in case of global cognition and there was a slight difference in terms of visuospatial abilities, attention, verbal intelligence and processing speed. The heterogeneity of the overall effect was contributed by some significantly moderating factors, such as comorbidities, neuropsychological domain and education. When BPD patients were compared with healthy controls, they could elicit cognitive impairment, decision making impairment, memory deficit, executive functioning impairment, processing speed impairment, verbal intelligence impairment, visuospatial abilities impairment, attention impairment. However the overall intellectual ability, non-verbal intelligence and language domains were not different. The cognitive performance was not affected by gender, age, race and antidepressant treatment. On the other hand, BPD patients with more education and parents of higher education had better performances. The cognitive performance of BPD patients with comorbidity with other personality disorders, i.e. major depression, eating disorders, any substance abuse disorders were worse, while comorbidity with anxiety disorders and post-traumatic stress disorder (PTSD) have not affected the results. The cognitive impairment observed in the patients is related to anomalies of brain structures and neurochemical changes. In BPD patients the impairment of executive function and decision making, the slight lack of attention can be related to previously experienced structural abnormalities (Irle et al., 2005; Rüsch et al., 2003), altered connectivity between brain regions (Minzenberg et al., 2007) and hypometabolism of the prefrontal cortex (De La Fuente et al., 1997; Juengling et al., 2003; Soloff et al., 2003). Impaired executive functions (difficulty in mental set shifting, planning, information updating and monitoring inhibition of prepotent responses) are associated with BPD symptoms like identity diffusion, irritability, impulsivity self injury, poor self control, emotional lability, dissociative symptoms, lack of self direction, rigidity, chronic feelings of emptiness and difficulty in shifting attention (Unoka & Richman, 2016).

In BPD patients the background of difficulties in decision-making may be the difficulty of retaining responses in order to get a greater reward (in impulsive spending sex, binge eating and substance abuse). There may be a connection between the delay aversion and processing disorder of punishment signals in reward situation, which may reflect a lack of balance between appetitive and aversive motivational states, when BPD patients received by confirmation signs. The same was found even in tasks where BPD patients received cognitive feedback about the negative consequences of their behavior (Svaldi et al., 2012; Unoka & Richman, 2016).

1.2. Learning and memory

The learning and memory are obligatory functions of the human brain which are needed in a normal life. These are necessary to survive the different challenges occurring in our life (Kandel et al., 2013). Weather deliberate or not, but we apply them in everyday life. Through this ability, we are able to better adapt to environmental changes, and they represent a great evolutionary advantage.

We call the processes during which knowledge is coded, stored, and then recalled as memory (Kandel et al., 2013). The segregation of memory and learning is difficult and always impossible. Berry and Dienes (1991) described that implicit learning and implicit memory can be interpreted as two independent concepts. They described that the characteristics of implicit memory processes were also characteristics of implicit learning. So the two phenomenon are not independent (Berry & Dienes, 1991). The same brain structures are involved in both functions (Packard & Knowlton, 2002; Squire et al., 2004; Squire & Zola, 1996).

1.2.1. The classification of memory

Memory can store and recall information what we need. Atkinson and Shiffrin (1968) described that memory can group into the following three parts: the sensory register, the short-term memory and the long-term memory.

The sensory register consolidates the sensory information only for a short time, and then the stored information could disappear. Short-term memory (also working memory) is the structure that gets input from the sensory register and the long-term

memory and it could store and change information. Working memory includes the immediate and small information that a person uses to perform cognitive tasks. The information hold here also disappears completely, but this is a longer time than in case of the sensory register. The timeframe is between one and 30 seconds (Atkinson & Shiffrin, 1968).

The long-term store is a constant storage place, even if the acquired knowledge has long been outside of consciousness (Kandel et al., 2013). The information hold here is from the short term storage. Long-term memory can be divided in two parts: the implicit (nondeclarative) and the explicit (declarative) memory (Graf & Schacter, 1985).

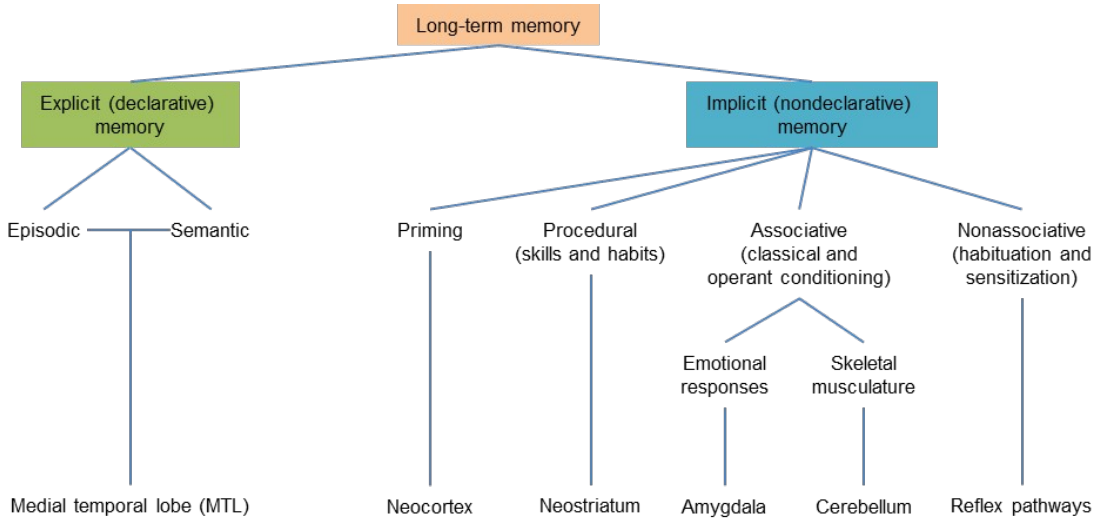

Fig. 2.
The structure of long term memory systems, and specific neural correlates.
From: Kandel et al., 2013

1.2.2.Explicit memory

Explicit long-term memory (declarative memory) is the processes that make it possible to consciously and voluntary recall previously hold information (Kandel et al., 2013). Two parts of explicit memory are the episodic and the semantic memories (Squire et al., 1993). Episodic memory is developed by a certain episode of life, or from autobiographical memory. Semantic memories are general facts and details of information absorbed over the years (Squire et al., 1993). Explicit memory is

functional and structural homogeneous. The center of it is the medial temporal lobe (MTL) and it is strongly connected to the hippocampi (Grafton et al., 1995; Hendelman, 2006; Squire et al., 1993).

1.2.3. The medial temporal lobe (MTL)

The main structure of declarative memory is the hippocampal formation of the MTL, which is a phylogenetically old structure. It contains the hippocampus, the dentate gyrus and the subicular region (Hendelman, 2006; Squire et al., 1993). The hippocampal formation has been found as the system of explicit encoding and retrieval of spatial memory as a cognitive map (O'keefe & Nadel, 1978). This formation gets information from all sensory modalities (Squire et al., 2004) and process multisensory integration, too (Lee et al., 2017). MTL has been described to important component of visual learning (Squire et al., 1993; Squire et al., 2004; Squire & Zola, 1996). The main projections of the hippocampus arrive from the entorhinal cortex and it could also get cortical input from the perirhinal and parahippocampal cortices. These cortices are connecting with frontal, temporal and parietal lobes and the retrosplenial cortex. The perirhinal and parahippocampal cortices are more important in terms of visual modality, getting input from unimodal and dorsal stream visual regions (Malkova & Mishkin, 2003; Squire et al., 1993; Squire et al., 2004; Squire & Zola, 1996). More structures are connected to the declarative memory including the prefrontal cortex (Ofen et al., 2007), the inferior temporal cortex (Squire & Zola, 1996) and the medial thalamus (Mayes, 1995). The organization of the explicit system can be seen on Fig. 3.

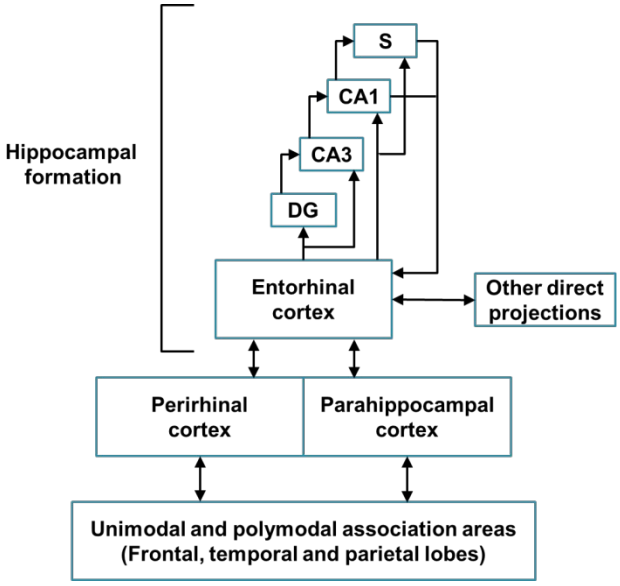

Fig. 3.
The organization of the explicit system.
Abbreviations: DG: dentate gyrus; CA: ammon's horn; S: subiculum. From: Squire et al., 2004

1.2.4. Implicit memory

Implicit long-term memory (nondeclarative memory) does not use conscious memory processes, but it could unconsciously affect thinking and behaving (Ellis, 2009; Graf & Schacter, 1985; Reber, 1989; Squire et al., 1993; Squire & Zola, 1996). Nondeclarative memory anatomically heterogenous and consists diverse systems. Nondeclarative memory is differs from the explicit memory several features. The first difference is the following: learning happens slowly and gradually. Secondly, the durability and reliability of the implicit memory is greater. And finally it is inflexible (Berry & Dienes, 1991; Squire et al., 1993). So that means that this process is very sensitive to environmental changes, the performance can be greatly reduced during the application of the acquired implicit knowledge (Bassili et al., 1989; Jacoby & Dallas, 1981). Nondeclarative memory is larger than explicit memory, so it is more resistant to neurological events (Schuchard & Thompson, 2014). This may be related to the fact that it is a phylogenetically older system (Reber, 1989) and it is a more diffused system than the explicit one (Squire et al., 1993).

1.2.5. Implicit memory functions

1.2.5.1. Priming

Priming is an improved state of recognizing and classifying different things, which are based on previous encounters with the same or similar things (Schacter & Buckner, 1998; Tulving & Schacter, 1990). For example, the brain processes an individual name or object faster when it is presented for the second time, regardless of whether we can recognize that the given object was seen before or not (Schacter & Buckner, 1998; Squire & Dede, 2015). The literature names two types of priming (Kandel et al., 2013). One of these is the conceptual type, which provides easier access to knowledge for semantic knowledge relevant to problem solving, since it was previously used by the individual. The other type is perceptual priming, which occurs in connection with a specific sensory modality (Tulving & Schacter, 1990).

1.2.5.2. Procedural learning

The procedural learning is the learning of a skill, habit or knowledge through repeated practice. This includes multiple learning such as motor and perceptual skills, e.g. mirror-drawing, mirror-reading and reaction time task (Cohen & Squire, 1980; Grafton et al., 1995; Heindel et al., 1989; Packard & Knowlton, 2002; Reber & Squire, 1998; Squire et al., 1993). This learning is mainly influenced by the integrity of the neostriatum (Grafton et al., 1995; Heindel et al., 1989; Knopman & Nissen, 1991; Knowlton et al., 1996).

1.2.5.3 Associative learning

The timing of the stimuli is important to make association during associative learning. The associative learning can divide into classical conditioning and operant conditioning (Fonyó, 2011; Kandel et al., 2013). During non-associative learning, the animal learns about the properties of a stimulus while during associative learning it learns the relationship between two stimuli, or the relationship between a stimulus and its own behaviour (Kandel et al., 2013).

a) Classical conditioning

Ivan Pavlov was the first who reported classical conditioning (stimulus-response theory) in animal experiments. During the process, the animal has to learn to associate two independent stimuli. One stimulus is the conditioned stimulus (can be visual, auditory, verbal, etc.) which initially does not elicit a response. The unconditioned stimulus could elicit an innate instinctive reaction that the animal performs without learning. If the conditioned stimulus is applied repeatedly close to the unconditioned one the response to unconditioned stimulus could be elicited to the new conditioned stimulus, too (Kandel et al., 2013). This type of learning is also intact in patients with amnesia, its development is not conscious (Clark & Squire, 1998; Gabrieli et al., 1995). It was established that this type of conditioning depends on the neuronal networks of the cerebellum and the brainstem (Thompson & Krupa, 1994; Thompson & Steinmetz, 2009).

b) Operant conditioning

The description of operant conditioning is attributed to Edgar Thomdike. It can also be called trial and error learning. It means the learning of the relationship between the certain behaviour and its consequences. A typical example in laboratory conditions is placing a hungry rat in a special test chamber, where the animal receives a reward for a given behaviour. For example, pushing a pedal results a positive reinforcement (e.g. food) immediately after the movement. Because of the positive reinforcement, it will push the pedal more and more often, it learns that pushing the pedal is followed by a reward. Sooner or later, the animal will probably push the pedal when it is hungry. During operant conditioning, the animal can receive not only positive but also negative reinforcement and some kind of punishment, too. In general, the animal tends to repeat behaviours that are followed by a reward, while behaviours that are aversive but not necessarily painful will not be repeated. The timing plays a critical role in both classical and operant conditioning. Classical conditioning is usually less successful if the time is elongated between the conditioned and unconditioned stimulus or if the unconditioned stimulus precedes the conditioned stimulus in time. During operant conditioning, the positive or negative reinforcement must come closely after the requested behaviour. If the animal receives reinforcement too late, the conditioning is only weakly achieved (Kandel et al., 2013).

1.2.5.4. Non- associative learning: habituation and sensitization

Non-associative learning occurs when an animal or person is exposed to a certain stimulus once or repeatedly. Habituation and sensitization are also common forms in everyday life. We speak of habituation when a harmless stimulus is repeatedly encountered and the response to this stimulus will be decreased. For example, you are celebrating the founding of the state on New Year's Eve, most people are startled by the sound of the first fireworks, however, as they hear more and more, get used to the noise and no longer react to it (Kandel et al., 2013).

In case of sensitization, the animal or person reacts with an increasing response to a stimulus, which will be presented after a strong or harmful stimulus. For example, an animal after a painful bite will react more vividly and decisively to a mild tactile stimulus. A sensitizing stimulus can overwrite the effect of habituation, which is called dishabituation (Kandel et al., 2013). In non-associative learning the timing of the stimulus is not fundamental.

1.2.5.5. Other types of associational learning

During category learning, the individual learns to organize objects, events or situations into different groups. This can be done on the basis of verbalizable properties (explicitly) or gradually, learned from stimulus pair to stimulus pair (implicitly) (Ashby et al., 1998; Ashby & Maddox, 2005).

Statistical learning means that we are able to perceive relevant patterns from the flow of information coming continuously from the environment. On the basis of this information we can predict with higher probability which stimulus follows the previously presented one (Batterink et al., 2019; Sáringer et al., 2022).

Acquired equivalence associative learning is a type of conditioning in which discrete and often different signals are linked together. This learning function is mainly associated with the frontostriatal loops of the basal ganglia and hippocampus (Myers et al., 2003a).

1.3. The basal ganglia

The basal ganglia consist of several interconnected subcortical nuclei, including caudate nucleus, the putamen, 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). Caudate nucleus and putamen form the neostriatum. The basal ganglia act primarily through cortico-basal ganglia-thalamo-cortical loops (Alexander & Crutcher, 1990; Alexander et al., 1986). The caudate nucleus, the main input structure of the basal ganglia receives glutamatergic afferents from all parts of the cerebral cortex. The STN could also receive direct cortical inputs (Parent & Hazrati, 1995). Different sensory information could also relay to the basal ganglia through the specific and non-specific relay nuclei of the thalamus (McHaffie et al., 2005; Nagy et al., 2003). The caudate nucleus and STN transmit signals to the GPi and the SNr. The GPi and the SNr transmit signals primarily to the thalamus (or the midbrain or the pons), which information will be relayed back to the cortex and limbic system. The internal circuits within the basal ganglia can be observed on Fig.4. (Alexander & Crutcher, 1990; Nambu, 2008). The basal ganglia consist of separate circuits with different tasks (Nambu, 2008). Between the prefrontal cortex and the dorsolateral caudate nucleus is the dorsolateral prefrontal circuit. The visual and auditory association cortical areas will be connected through the lateral orbitofrontal circuit with the ventromedial caudate body. The anterior cingulate circuit binds the limbic system (hippocampus, amygdala, entorhinal and perirhinal cortices) and the ventral striatum. These circuits could contribute to in implicit learning functions (Alexander et al., 1986; Nambu, 2008; Packard & Knowlton, 2002). The basal ganglia take part in reward-driven mechanisms by the dopaminergic SN-striatum connection and by the ventral tegmental area (VTA) hippocampus pathway, too (Delgado, 2007).

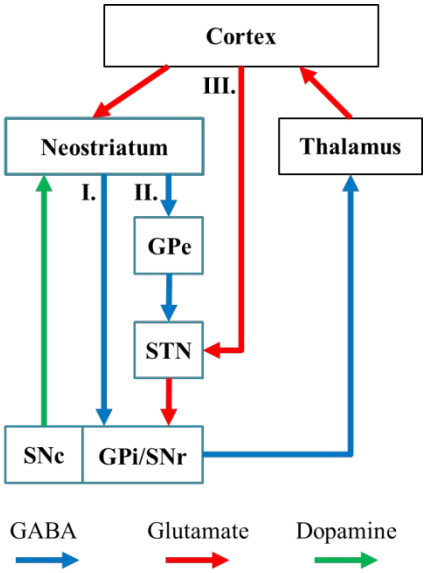

Fig. 4.
The structure of the basal ganglia circuitry.
Abbreviations: GPe, GPi: external and internal part of globus pallidus; SNr, SNc: substantia nigra pars reticularis and compacta; STN: subthalamic nucleus. The roman numbers indicate the three main routes (I: Direct or "Go" pathway, II: Indirect or "non-Go" pathway, III: hyperdirect pathway) of the circuitry.

1.3.1. The cognitive functions of basal ganglia

The basal ganglia are not only involved in motor behavior, but especially the dorsal striatum is involved in learning and memory processes. One of the main hypotheses is that they engage in stimulus-response based learning. In the case of basal ganglia impairment many cognitive performances are reduced (for review see (Glosser, 2001). Cell loss observed in the caudate nucleus and putamen in Huntington's disease is related to cognitive impairment. In Parkinson disease, reduced striatal functions was also found as a consequent of the cell death in the substantia nigra. In both neurological diseases, the motor deficit is the clearest, but alterations in learning and memory functions are also obvious. The damage of the caudate nucleus in experimental animal model elicits analogous habit learning deficits as in humans with basal ganglia disorders. The basal ganglia are also involved in sequence learning (e.g. Laforce & Doyon, 2001; Willingham et al., 1996) and in visuomotor sequence learning (Nissen & Bullemer, 1987; Reber & Squire, 1994). The neuropsychological and human neuroimaging studies found that the basal ganglia are involved in learning skills and habits. The reading of mirror-reserved text is coupled to the enhanced

activation of the caudate nucleus (Dong et al., 2000). Similarly enhanced caudate nucleus activation was demonstrated in the serial reaction-time task (Doyon et al., 1996; Rauch et al., 1997). All studies investigating the basal ganglia during degenerative disease support the role of the basal ganglia in habit learning.

1.4. Acquired Equivalence learning

Acquired equivalence is a specific kind of associative learning. During acquired equivalence learning the participants have to learn to associate two or more different stimuli (antecendents) base on their same outcomes (consequents). Because they have same outcomes, they are equivalent (Meeter et al., 2009; Myers et al., 2003a; Ward-Robinson & Hall, 1999). Due to the development of equivalence between the antecedent stimuli, participants will be able to apply the learned associative rule on new pairs of stimuli that have not been presented before, the development the equivalence thus promotes the success of generalization (Bonardi et al., 1993; Myers et al., 2003a). The visual testing paradigm, the Rutgers Acquired Equivalence Test (RAET) was developed by Myers and colleagues (Myers et al., 2003a), can be divide into two phases, an acquisition phase where the persons establish the equivalence between certain stimuli, and a test phase, where they have to recall the learned stimulus pairs and apply and generalize the association regularities to build new stimulus pairs. These two phases are primarily related to the functioning of two different brain structures. The learning phase is primarily related to frontostriatal loops and to the functions of the basal ganglia, and the test phase is primarily related to the functioning of the hippocampus and mediotemporal lobe (Meeter et al., 2009; Myers et al., 2003a).

To support this, Myers and colleagues (2003a) examined patients with Parkinson's disease and hippocampal atrophy. Patients with Parkinson's disease performed worse in the learning phase than healthy controls but the retrieval and generalization functions were not altered in Parkinson patients. On the other hand, patients suffering from hippocampal atrophy showed similar performance to the control group in the learning phase, but in the test phase, especially in the generalization tasks, they performed worse (Myers et al., 2003a). Furthermore, the RAET was previously applied in other neurological and psychiatric disorders, i.e.

Alzheimer's disease, schizophrenia, obsessive-compulsive disorder (OCD), Tourette syndrome and migraine without aura (Bazanis et al., 2002; Bódi et al., 2009; Giricz et al., 2021; Kéri et al., 2005; Myers et al., 2003a; Öze et al., 2017; Pertich et al., 2020).

1.5. Effect of multisensory stimuli on learning

The basal ganglia and the hippocampi, the key structures involved in equivalence learning process multisensory information (Bates & Wolbers, 2014; Nagy et al., 2005; Nagy, et al., 2006; Ravassard et al., 2013). This concept raises the idea to check the audiovisual associative learning as well. It is a generally accepted fact that multisensory information has additional meaning compared to the sum of some unimodal information (Nagy et al., 2006; van Atteveldt et al., 2014). Multisensory information processing plays a role in orientation and in the recognition of social objects, it can also affect reaction time and response accuracy (Hershenson, 1962; Patching & Quinlan, 2004; Regenbogen et al., 2015). The extra information appears at different levels of brain function. It can even be observed at the single-cell level in many brains areas (Chudler et al., 1995), such as the superior colliculus (Wallace et al., 1998), the basal ganglia (Nagy et al., 2006; Reig & Silberberg, 2014) and cortex (Minciacchi et al., 1987), but also at the level of behavior (Godfroy-Cooper et al., 2015; Lanz et al., 2013). Multisensory integration can occur between stimuli of different modalities, for example visual and auditory (Patching & Quinlan, 2004; Sakata et al., 2004), visual and vestibular (Deshpande & Patla, 2005), auditory and tactile (Leonardelli et al., 2015), or between auditory, visual and somatosensory stimuli (Diederich & Colonius, 2004; Nagy et al., 2006; Wang et al., 2012).

2. Aims of the study

The primary aim of the present thesis work was to investigate the visually-guided associative acquired equivalence learning and connected memory processes in patients with borderline personality disorder (BPD). This question is significant because the applied cognitive test could shed light on the function of the basal ganglia and the hippocampi in learning processes, the brain structures, which are clearly involved in the pathophysiology of the BPD. The question was, whether the BPD affects the associative acquired equivalence learning and connected memory processes. Specific question was whether there are any differences in the performances of the BPD patients in different phases of the paradigm, i.e. in acquisition and/or in retrieval and/or in the generalization parts of the test phase.

Both of structures, the basal ganglia and the hippocampi, which are the primary target structures of the sensory-guided associative learning process not only visual but multisensory (audiovisual) information. This is the base of the second main aim of the study to develop and to validate a new multisensory, audiovisual equivalence learning test, which will be suitable for the further investigation of the learning processes not only in the BPD patients but in other patients with neurological and psychiatric disorders connected to the dysfunction of basal ganglia and the hippocampi.

3. Materials and methods

3.1. Participants

In line with the aims we present in this PhD thesis the results of two studies. Twenty-three BPD patients and the matched healthy controls were investigated in the first study (see the results in Rosu and colleagues, 2022, Heliyon). In the second study (see the results in Eördegh and colleagues, 2019, PLoS One) 151 healthy adult controls were investigated with the own-developed multisensory test in the audiovisual equivalence learning study. All participants were Caucasian race. To exclude color blindness in the patient and matched healthy control groups, the intactness of color vision was evaluated using Ishihara plates prior to testing. Only patients and controls with normal color vision were included in the current studies. All of them were informed about the background, aims and the procedures prior to involve of the study. All patients received no financial benefit or another any compensation for participation. All participations free of any ophthalmological, otological, neurological and psychiatric (except study#1, BPD) conditions were eligible. The diagnosis of BPD was made by board certified psychiatrists according to the DSM-5 at the hospital. Each participant signed an informed consent form. Both study protocols conformed to the tenets of the declaration of Helsinki in all respects, and it was approved by the Regional Ethics Committee for Medical Research at the University of Szeged, Hungary (50/2015-SZTE).

3.1.1. Study#1

Altogether 23 BPD patients (and the matched healthy controls) participated in this study. All of the patients were diagnosed with borderline personality disorder (18 women and five men, mean age: 28.9 ± 9.6 [range: 18–55] years, median education level: 3.0 [range: 1.0 – 4.0]). We examined their educational levels: 1–elementary school, 2–secondary school, 3–high school, 4–university. The patients were recruited from the Department of Psychiatry (Albert Szent-Györgyi Medical School, University of Szeged). The diagnosis of BPD was made by board certified psychiatrists according to the DSM-5 at the hospital. Inpatients and outpatients were diagnosed with borderline personality disorder without any other psychiatric comorbidities. Eight patients didn’t receive any medication, 15 patients used drugs (unchanged) in order to be stable and to balance the symptoms. To investigate this patient group 23 healthy

control humans from our database were fitted in sex, age and education level (18 women and five men, mean age: 28.7 ± 9.2 [range: 18 – 53] years, median education level: 3.0 [range: 2.0 – 4.0]). It is worth to declare that in BPD and healthy control populations were no significant differences in demographic data. (Kruskal-Wallis test, $p > 0.05$) (Table 1.).

Group	Number of cases	Female/Male	Age, mean (years)	Age, range: (years)	Educational level median (range)
All patients	23	18/5	28.9±9.6	18-55	3.0 (1.0-4.0)
Matched controls	23	18/5	28.7±9.2	18-53	3.0 (2.0-4.0)
Medicated patients	15	12/3	31.2±10.7	18-55	3.0 (1.0-4.0)
Matched controls to medicated patients	15	11/4	30.7±10.1	18-53	3.0 (2.0-4.0)

Table 1.
The demographic data for the patient and the control groups

3.1.2. Study#2

In line with the second aim of the study 151 healthy adult volunteers were involved in the audiovisual equivalence learning test. All of the participants were free of any ophthalmological, ontological, neurological and psychiatric disorders.

3.2. Equivalence Learning Paradigms

The tests were run on laptops (Lenovo T430, Fujitsu Siemens Amilo Pro V3505, Samsung Electronics 300e4z/300e5z/300e7z, Lenovo Yoga Y500), and the

participants used headphones (Sennheiser HD 439 closed) for multisensory testing. The participants sat at a comfortable distance (114 cm) from the computer screen in a quiet room. One patient was tested at a time without any time limit, so the patients could concentrate and attention to learning. Quick responses were not expected.

3.3. Procedure

The paradigms were visual and multisensory (audiovisual) guided acquired equivalence learning tests. Both paradigms have two main phases, the acquisition and the test phase. During the learning process (acquisition phase) in the visual test on the computer screen appeared a graphic face and two different colored graphic fish. The patients had to choose, that which of the fish was connected with the given face by pressing the LEFT or RIGHT keys of the keyboard. In the first phase of the paradigm the computer gave feedback whether the choices were correct or no. When a green mark was appeared on the screen, this means that the choice was good, when a red mark was on the screen that means that the answer was wrong (Fig. 5).

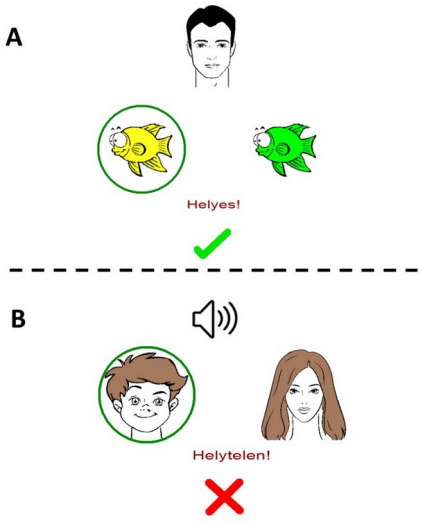

Fig. 5.
Schematic drawing of the acquisition phase of the applied visual and audiovisual guided associative learning paradigms with feedback.
"Helyes" means correct, "Helytelen" means incorrect.

The computer generated possible associations randomly. There were four possible faces: male, female, male child and female child (A1, A2, B1, B2). The four fish have different colors: blue, red, yellow and green (X1, X2, Y1, Y2). In this

example when A1 or A2 face appeared on the screen the good answer was X1 fish, when B1 and B2 were on the screen the good choice was Y1 fish. So, in these face-fish associations the participants had to learn that A1 face is equivalent with A2 face, then B1 is also equivalent with B2 too. In the next steps the participants had to learn new associations, when they have seen A1 face, they had to mark X2 fish, and when they have seen B1 face, the correct answer is Y2 fish. In detail, the participants had to achieve 4 consecutive correct responses after the presentations of the first two associations (A1 and X1, B1 and Y1). After these increasing of consecutive correct answers (6, 8, 10, 12 after introduction of each new association, respectively) needed to proceed. If the participants have learned all of the hitherto presented associations (a certain number of correct answers), they could proceed to the next step. Because of this the length of the association phases and the number of trials in this phase varied among the participants, depending upon how efficiently they learned. Thus, the number of trials during acquisition depends on the effectiveness of the associative learning. When all associations were successfully completed, the test phase (retrieval and generalization) started where the computer gave no more feedback about the choices.

In the test phase of paradigms (retrieval and generalization) new unknown but predictable associations appeared randomly mixed with the previously learned associations. The test phase contained 48 trials, from which 36 trials were already learnt pairs (retrieval part) and 12 were new unknown pairs (A2, X2; B2, Y2, generalization part) (Fig. 6.).

The structure of multisensory (audiovisual) paradigm was the same as the visual paradigm (Fig. 7.). Clearly-distinguishable sounds (a cat's meow, the sound of an ignition key, a note played by a guitar and a woman saying a Hungarian word with neutral emotional tone) served as antecedents (sound 1, sound 2, sound 3, sound 4) and faces were used as consequents (X1, X2, Y1, Y2). In each trial a sound (SPL = 60 dB) was played and two faces were presented to the participants on computer screen, who had to learn which face goes with which sound. The stimuli were presented at the same time on the computer screen and through a closed headphone. The participants were asked to choose which face (left or right) is coupled with the given sound and were asked to press the corresponding button (left or right) on the keyboard. The auditory and visual components of the multisensory stimulus pairs were primarily

semantically incongruent (except in the unfortunately case of a woman's voice being matched with a woman's face) (Table 2.).

ACQUISITION			TEST	
Shaping	**Equivalence training**	**New consequents**	**Retrieval**	**Generalization**
A1 -> X1	A1 -> X1	A1 -> X1	A1 -> X1	
	A2 -> X1	A2 -> X1	A2 -> X1	
		A1 -> X2	A1 -> X2	
				A2 -> X2
B1 -> Y1	B1 -> Y1	B1 -> Y1	B1 -> Y1	
	B2 -> Y1	B2 -> Y1	B2 -> Y1	
		B1 -> Y2	B1 -> Y2	
				B2 -> Y2

Table 2.
A summary of the visual and the audiovisual associative learning paradigms
A, B: antecedents (faces), X,Y: consequents (fishes). See the detailed description in the text.

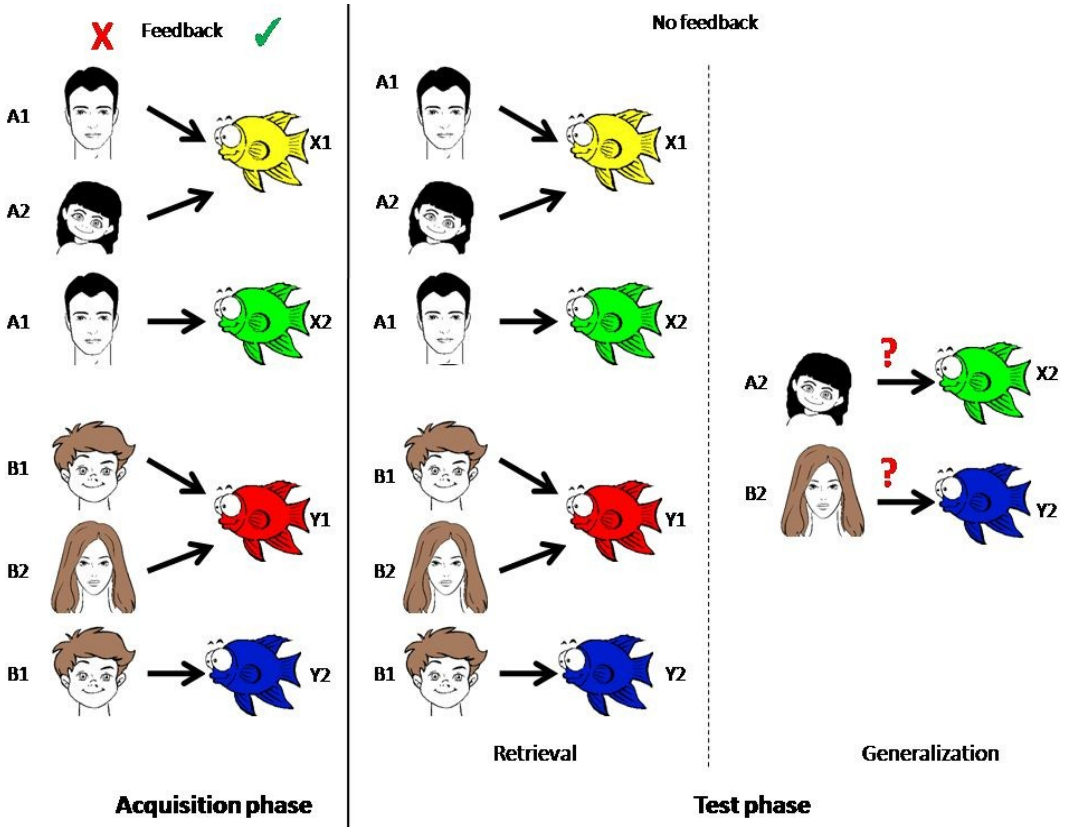

Fig. 6.
The schematic drawing of the applied visually guided associative learning paradigms

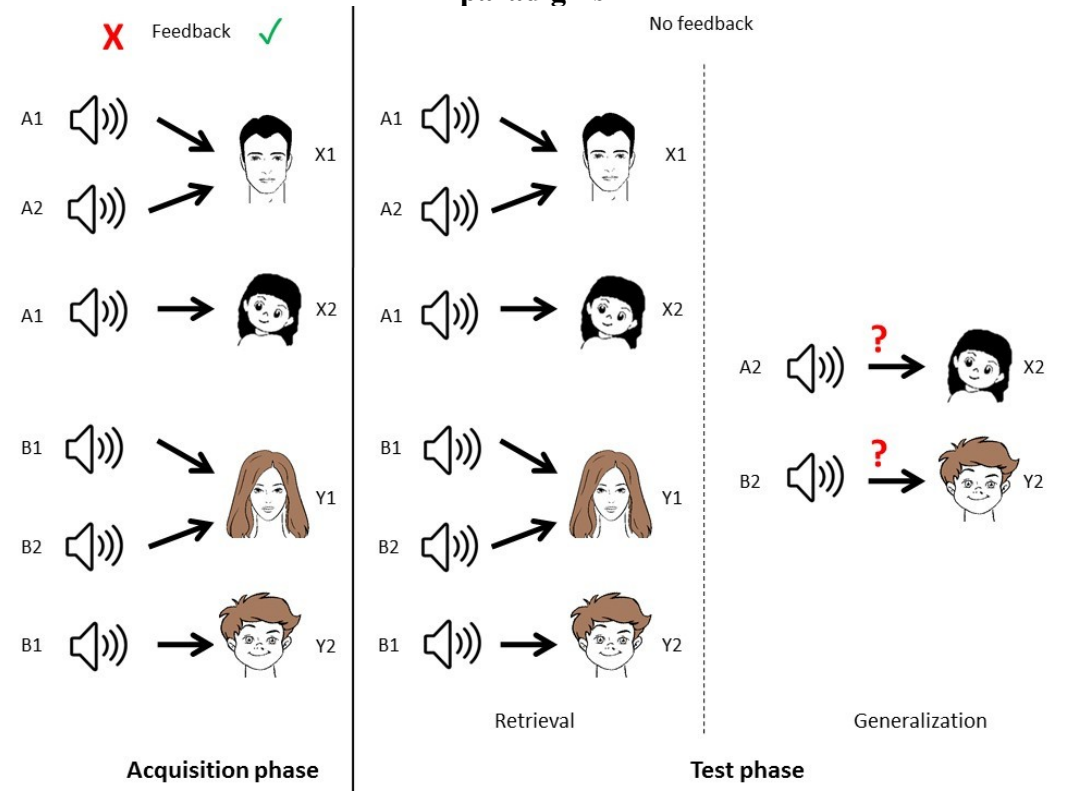

Fig. 7.
The schematic drawing of the applied multisensory (audiovisual) guided associative learning paradigms

3.4. Statistical analysis

In the acquisition phase, the number of trials and the answer accuracy were registered. In addition, the number of accurate response (retrieval and generalization) was assessed for known and unknown associations in the test phase. Based on these data, the error ratios were calculated by dividing incorrect answers by all the choices. The Association phase learning error ratio (ALER) and number of trials (NAT) in the acquisition phase, retrieval error ratio (RER), and generalization error ratio (GER) in the test phase were assessed and compared between the BPD patients and the matched healthy control group. The reaction times (RT) is defined as the time between the appearance of the stimuli and the response of the participant (pressing the LEFT or RIGHT button). RTs were compared between the two groups. Reaction times (RT) in each phase for each answer were measured in ms with ms accuracy. Only the RTs of correct answers were analyzed. The RTs were kept only within 3SDs of participants' average.

First, we tested the distribution of our data. The data sets did not have a normal distribution according by the Shapiro–Wilk test. Thus, the performance and reaction times between the BPD patients and the matched healthy control group were compared with Mann–Whitney U test. The performances and reaction times between the visual and multisensory paradigms in the healthy control group were compared using the Wilcoxon match paired test.

To avoid a carry-over effect between the visual and audiovisual paradigms in the multisensory study, the different paradigms were recorded in a random order among the participants.

The statistical analysis was performed in Statistica 13 (Dell Inc. USA) and G*Power 3.1.9.2. (Düsseldorf, Germany).

4. Results

4.1. Study#1

In this study, we analyzed the cognitive equivalence learning abilities of patients with DPD without any otological, opthalmological, neurological, or psychiatric comorbidities (n = 23). All patients could complete the whole visually guided acquired equivalence learning paradigm.

4.1.1. Comparison of the BPD and matched healthy control groups

In the acquisition phase of the paradigm, the BPD group had a significantly worse performance than the matched healthy control group (Fig. 8.).

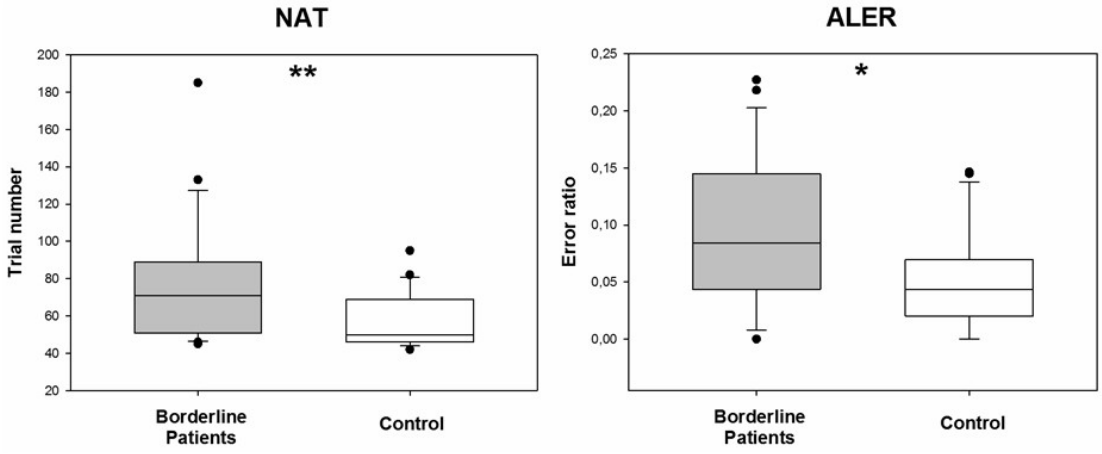

Fig. 8.
Performances of BPD patients and healthy controls in acquisition phase of visually guided acquired equivalence paradigm
NAT denotes the number of required trials in the acquisition phase of the paradigm. Acquisition learning error ratio (ALER) represents the error ratios in the acquisition phase of the paradigm. The gray color indicates the performances of patients with borderline personality disorder in each panel. Meanwhile, the white color shows those of matched healthy controls. The lower margin of the boxes represents 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 denote the 90th and 10th percentiles, respectively. The dots over and under the whiskers indicate the extreme outliers. The two black stars denote extremely significant differences ($p > 0.01$), and the black star significant differences ($p > 0.05$).

The median NATs of the BPD patients and matched healthy control groups were 71.0 (range: 45.0 – 185.0) and 50.0 (range: 42.0 – 95.0), respectively (Mann–Whitney test U = 146.5, p = 0.0098, effect size = 0.8077, power = 0.9525). The median ALERs were 0.084 (range: 0.0 – 0.227) and 0.043 (range: 0.0 – 0.15) for the BPD patients and matched healthy control groups, respectively (Mann–Whitney test U = 162.5, p = 0.0255, effect size = 0.7845, power = 0.9520). However, the reaction times of the two groups in the acquisition phase did not differ significantly. The median reaction times were 1565 ms (range: 1035 – 3402 ms) and 1675 ms (range: 1070 – 3489 ms) for the BPD patients and matched healthy control groups, respectively (Mann–Whitney test U = 256, p = 0.860). In contrast to the acquisition phase the performances of the BPD group were not different from those of the matched healthy controls in the retrieval and generalization parts of the applied visual associative learning paradigm (Fig. 9.).

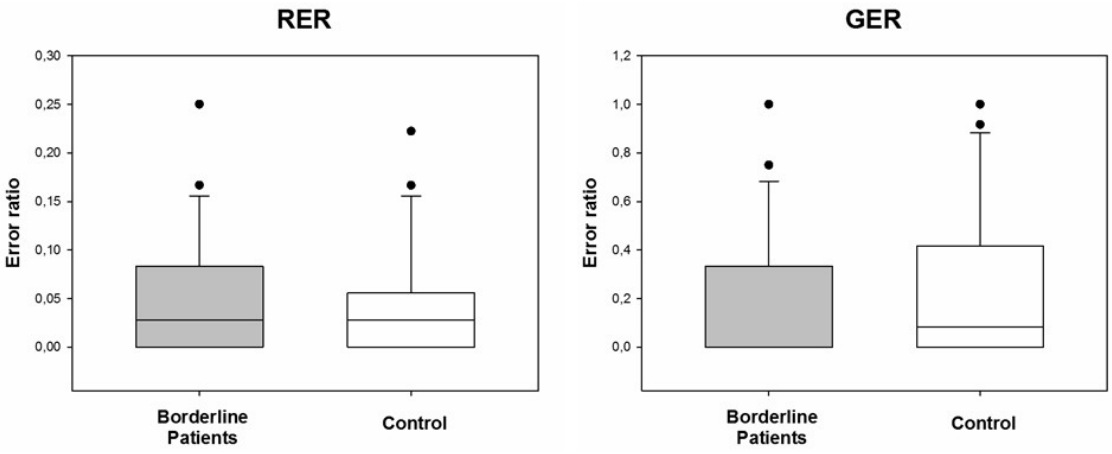

Fig. 9.
Performances of BPD patients and healthy controls in test phase of visually guided acquired equivalence paradigm
The diagrams denote the error ratios in the retrieval (RER) and generalization (GER) parts of the test phase. In each panel, the first boxplot (gray) shows the performance of the borderline personality disorder group, and the second boxplot (white) the performance of the matched healthy control group. The other conventions are similar as on Fig. 8.

The median RERs were 0.028 (range: 0.0 – 0.25) for the BPD group and 0.028 (0.0 – 0.22) for the matched healthy control group (Mann–Whitney test U = 216, p =

0.275). The median GERs were 0.00 (range: 0.0 – 1.0) and 0.083 (range: 0.0 – 1.0) for the BPD patients and matched healthy control groups, respectively (Mann–Whitney test U = 220, p = 0.307). The reaction times of the two groups in the retrieval and generalization parts were also not different. During the retrieval part of the test phase, the median reaction times of the BPD group and matched healthy control group were 1934 ms (range: 1107 – 3729 ms) and 1694 ms (range: 1145 – 2838 ms), respectively (Mann–Whitney test U = 258, p = 0.895). In the generalization part, the median reaction times were 2213 ms (range: 1224 – 8549 ms) for the BPD group and 2310 ms (range: 1159 – 10883 ms) for the matched healthy control group (Mann–Whitney test U = 235, p = 0.879).

4.1.2. The effect of medication on the performances of BPD patients in visually-guided equivalence learning

In a short sentence can be summarized that the medication did not affect significantly the performances of the BPD patients in visually guided equivalence learning. In the acquisition phase of the paradigm, the performances of the medicated group did not differ from those of the non-medicated group. The median NATs of the medicated and non-medicated groups were 69.0 (range: 45.0 – 133.0) and 80.0 (range: 46.0 – 185.0), respectively (Mann–Whitney test U = 47, p = 0.4196). The median ALER values were 0.077 (range: 0.0 – 0.218) for the medicated group and 0.117 (range: 0.043 – 0.227) for the non-medicated group (Mann–Whitney test U = 36, p = 0.129).

Similarly, to the acquisition phase, the medicated and non-medicated groups did not differ in terms of performances in the retrieval and generalization parts of the test phase. The median RERs were 0.028 (range: 0.0 – 0.167) for the medicated group and 0.056 (range: 0.0 – 0.250) for the non-medicated group (Mann–Whitney test U = 48.5, p = 0.468). The median GERs were 0.00 (range: 0.0 – 1.0) and 0.00 (range: 0.0 – 0.750) for the medicated and non-medicated groups, respectively (Mann–Whitney test U = 56.5, p = 0.830).

4.2. Study#2

Altogether 151 healthy volunteers participated in this study. Only a small minority of the participants (6/151) did not complete both the visual and audiovisual (multisensory) paradigms**.** After the further exclusion of the extreme outliers (outliers were determined 3SD above the mean in trial number and in reaction times) in the learning performances, 141 volunteers were analyzed in detailed in both the visual and the audiovisual paradigms (n_{male} = 41, age: 31.21 ± 11.51 years, range: 18 - 72 years).

4.2.1. The performance in the visual and multisensory paradigms

The median NAT necessary to learn the visual paradigm was 57 (range: 41-269, n = 141), and in the case of the multisensory paradigm it was 56 (range: 41 - 226, n = 141).

In the visual paradigm the median ALER was 0.06 (range: 0 - 0.3333) and in the multisensory paradigm it was similarly 0.06 (range: 0 - 0.3469). These values in acquisition phase didn't differ significantly (NAT Wilcoxon Matched Pairs Test Z = 0.787, p = 0.431; ALER Wilcoxon Matched Pairs Test Z = 0.217, p = 0.828). In the retrieval part of the test phase the RER was moderate (median: 0.02778, range: 0 - 0.4167) in the visual paradigm and it was the same in the multisensory paradigm (median: 0.02778, range: 0 - 0.4167). This difference was also not significant (Wilcoxon Matched Pairs Test Z = 1.057, p = 0.290). The same trend can be observed in the generalization part of the test phase among the GERs. In the visual and multisensory paradigms the GER median were 0.08333, (range: 0 - 1) and 0 (range: 0 - 1), respectively, (Wilcoxon Matched Pairs Test Z = 1.831, p = 0.067).

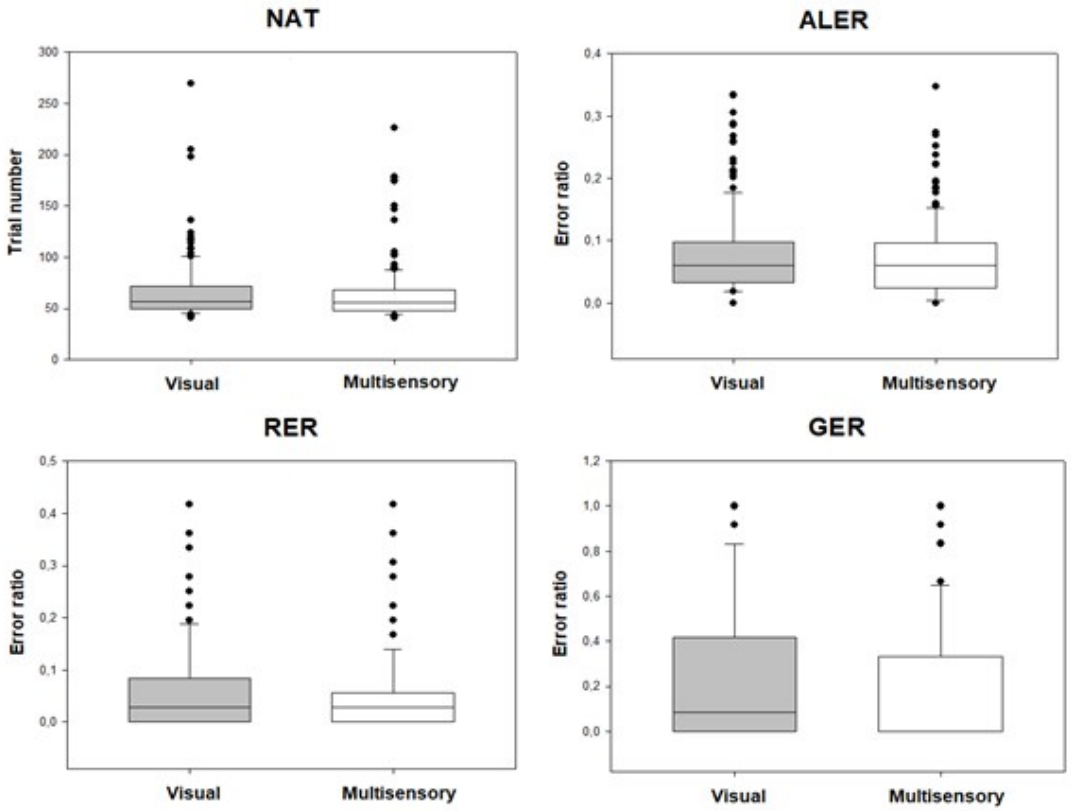

Fig. 10.
Performances in the sensory guided equivalence learning paradigms.
(NAT) denotes the number of the necessary trials in the acquisition phase of the paradigm. (ALER) shows the error ratios in the acquisition phase of the paradigm. (RER) and (GER) denote the error ratios in the retrieval and generalization parts of the test phase, respectively. In each panel, the first column (light grey) shows the results in the visual paradigm and the second column (white) demonstrates the results in the multisensory (audiovisual) paradigm. The lower margin of the boxes indicates the 25th percentile, the upper margin the 75th percentile, while the line within the boxes marks the median. The error bars (whiskers) above and below the boxes are the 90th and 10th percentiles, respectively. The dots over and under the whiskers represents the extreme outliers.

4.2.2. Latency of the correct trials in the two paradigms

Fig. 11. denotes the mean latencies of the correct trials in the acquisition phase and in the retrieval and generalization parts of the test phase in the visual and the audiovisual paradigms.

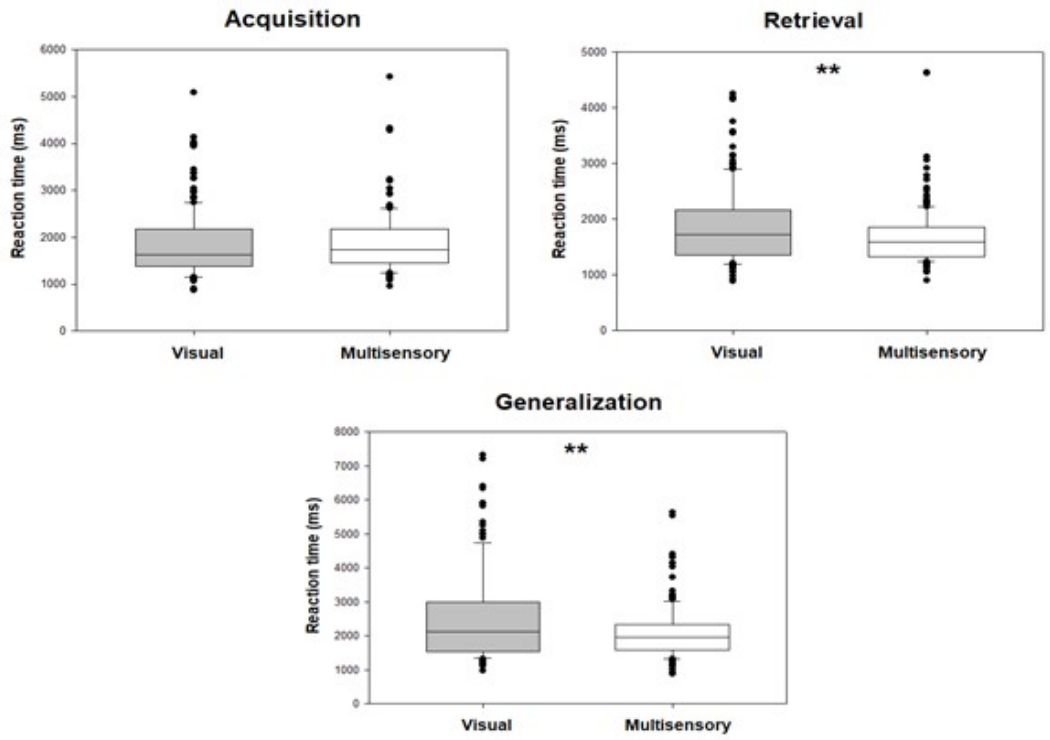

Fig. 11.
Response latencies in the sensory guided equivalence learning paradigms.
The ordinates show the latencies in millisecond (ms). Other conventions are the same as in Fig. 10.

We compared the latency of the correct trials among the same phases of the different paradigms. The median latency of the visual and the multisensory correct trials in the acquisition phase were not significantly different (median: 1729 ms, range: 954 - 5423 ms then visual correct trials (median: 1631 ms, range: 866 -5084 ms, n = 141, Wilcoxon Matched Pairs Test Z = 0.588, p = 0.557) (Fig. 11.).

In contrast to the acquisition phase, the median latencies of the correct trials in the two tests differed significantly in the retrieval and the generalization parts of the test phase. The median latency of the visual correct trials was significantly longer (median: 1720 ms, range: 881-4250 ms, n = 141), then that of the multisensory correct trials (median: 1583 ms, range: 894 - 4626 ms, n = 141, Wilcoxon Matched Pairs Test Z = 3.426, p = 0.0006, Fig. 11.). In the generalization part of the test phase was the median latency longer in the visual paradigm (median: 2122 ms, range: 966 - 7314 ms, n = 138) than in the audiovisual (median: 1952 ms, range: 883 - 5638 ms, n = 141, Wilcoxon Matched Pairs Test Z = 2.743, p = 0.006, Fig. 11.).

5. Discussion

This study was the first, which examined the visually guided associative learning abilities of BPD without any comorbidities. We asked whether this mental health disorder could affect equivalence learning and related memory processes. The Rutgers Acquired Equivalence Test (Myers et al., 2003a) was originally developed to learn about the visually guided associative learning of neurological patients with dysfunction of the basal ganglia and the hippocampi. The applied equivalence learning test requires the frontostriatal networks and the hippocampi (Myers et al., 2003a). Thus the dysfunction of these structures could elicit functional cognitive alterations in BPD patients. Implicit and explicit memory functions have been studied in BPD, but the results are not clear and strongly controversy. These results observed that there are no alterations in implicit statistical learning (Hornung et al., 2008) and procedural memory processes, which are connected to the function of the basal ganglia in BPD (Beblo et al., 2006). On the other hand, Mensebach and colleagues (2009) found dysfunction in visually guided functions like visual memory, visuospatial abilities and executive functions in BPD patients (Mensebach et al., 2009). Regarding explicit memory the functional magnetic resonance imaging (fMRI) study did not observe differences in episodic and semantic memory, although greater cortical operation was needed to archive similar performance (Ruocco & Bahl, 2014). BPD patients did not show decreased verbal or visual episodic memory (Rentrop et al., 2008), however, these patients performed worse in the Go/No-go task, which pointes damage in response inhibition (Myers et al., 2003b). Several studies described earlier that the basal ganglia are involved in the pathogenesis in BPD (Fineberg et al., 2018; Lamers et al., 2019; Stewart et al., 2019; Wang et al., 2017). Increased gray matter volume was found in BPD patients, too (Ruocco et al., 2013; Schulze et al., 2016). Aguilar-Ortiz (2018) did not observe any changes in the in the hippocampus while other areas were affected. The cortical volume reduction was found in the dorsolateral prefrontal cortex bilaterally and in the pregenual medial frontal cortex (Aguilar-Ortiz et al., 2018).

Our results demonstrated functional alterations in the equivalence learning of the BPD patients. In the acquisition phase of the paradigm the participants have to make associations between two visual stimuli, which primarily point the intactness

function of basal ganglia (Myers et al., 2003a; Packard & Knowlton, 2002; Shohamy & Wagner, 2008; White, 1997). Similarly to the BPD patients the performance was significantly decreased in other neurological or psychiatric conditions, i.e. Parkinson's disease (Myers et al., 2003a), Tourette syndrome (Moustafa et al., 2009) and adult migraine (Öze et al., 2017), which diseases are connected at least partially to the impairment of the basal ganglia. Our results demonstrated that BPD patients have impairments in visually guided associative learning abilities. The results in acquisition phase (NAT, ALER), when the participants have to learn associations, pointed out that BPD patients have difficulties with making association from two independent stimuli. These results may be explained as a behavior indicator of the earlier described basal ganglia dysfunctions in BPD.

On the other hand, in the test phase where the connected memory processes (retrieval and generalization) were investigated were no alterations in the BPD patient group. In the second phase the participants had to recall already learned (retrieval) and build new, unknown associations (transfer, generalization), which function mainly points the functions of the hippocampus and the mediotemporal lobe (Myers et al., 2008; Opitz, 2014; Shohamy & Wagner, 2008). The performances were not reduced, which could suggest normal hippocampal functions in BPD. In contrast, reduced performances were found in the retrieval and the generalization functions in patients with hippocampus-mediotemporal lobe injury (Myers et al., 2003a; Ullman & Pullman, 2015), Alzheimer's disease (Bódi et al., 2009), and adult migraine (Öze et al., 2017), which diseases are connected at least partially to the impairment of the hippocampus-mediotemporal lobe.

In case of the reaction times there were no differences between the BPD patients and healthy controls in the whole learning paradigm. Rentrop and colleagues (2008) found that the reaction times can be significantly shorter in BPD and stem from impaired response inhibition of BPD patients. Arose that the impaired response inhibition could cause the impaired performance in the acquisition phase, but the unaffected reaction times in equivalence learning results do not support this.

One limitations of the BPD study must be taken into account. This is the relatively low number of participants in the study. Altogether 23 BPD patients were included, which can be partly attributed to the strict use of criterions of the DSM-5 and the exclusion of patients with alcohol and drug abuse problem and other neurological and psychiatric comorbidities. However, despite this limitation, our research had a

significant advantage. That is, that this research analyzed associative learning in patients with clear BPD without any other comorbidities. Thus we can surely see in our sample the effect of BPD on the visual associative learning and the connected memory processes and other neurological or psychiatric comorbidities could not influence the results. Notably, the relatively small sample size could limit generalizability of the results. Moreover, the results have large statistical power and effect size value. Hence, they might be generalized beyond the population assessed. Another concern was whether the medications might influence the performance of BPD patients. The psychophysical results (NAT, ALER, RER, and GER) of the medicated and non-medicated groups were compared. However, there were no differences in terms of the investigated parameters between the medicated and non-medicated groups. Therefore, medicines had no or only minor influence on the performances in visual associative learning and connected memory processes in BPD patients.

In summary, our result in line with previous neuroimaging studies and could confirm the involvement of the basal ganglia in BPD. On the other hand, the hippocampi mediated memory processes were not altered in borderline personality disorder.

It is well known from earlier studies that both brain structures fundamentally involved in visual associative learning, the basal ganglia and the hippocampi receive not only visual but also multisensory information (Bates & Wolbers, 2014; Nagy et al., 2005; Nagy et al., 2006; Ravassard et al., 2013). A bimodal or multimodal information could be more informative in its complexity than a unimodal stimulus from the environment. Having realized, though, that we did not have normative data about the modality-dependence of the equivalence learning we aimed to develop and introduce a multisensory (auditory-visual)-guided equivalence learning paradigms in order to compare the performance of healthy volunteers in visual and audiovisual (multisensory) tasks. A specific aim of this development was to produce a new cognitive test, which could be suitable to check the learning abilities of neurological and psychiatric patients later. Special intention was played to the multisensory-guided learning whether the earlier described multisensory integration can be found in behavioral level during multisensory-guided acquired equivalence learning.

Multisensory integration could contribute to sensorimotor processes but also to cognitive functions. This multisensory facilitation has a role in visual perception

(Frassinetti et al., 2002) object recognition (Fort et al., 2002; Suied et al., 2009) emotional change recognition (Chen et al., 2016), face and voice recognition (Love et al., 2011), or person recognition (Joassin et al., 2011). The multisensory information influenced the reaction time and accuracy of answers (Hershenson, 1962; Miller, 1982; Patching & Quinlan, 2004).

Our research group developed a multisensory (audiovisual) version (SoundFace test) of the original visually guided acquired equivalence associative learning test (RAET). Our research was the first examination of the multisensory associative learning functions of basal ganglia and hippocampi in healthy humans (Eördegh et al., 2019). We have firstly applied after the validation of this test in neurological and psychiatric patient populations, too (Giricz et al., 2021; Pertich et al., 2020). The study of Eördegh (2019) examined the performances and the RTs of healthy individuals in visual and multisensory guided associative learning paradigms. The paradigm can be divided into two phases regardless of modality. The first is the acquisition phase in which the participants have to learn visual and multisensory stimulus combinations based on feedback. Our results demonstrated that the multisensory stimuli could elicit not better performances in the acquisition phase than the unimodal ones. Thus, the modality of the stimuli does not influence the performance in acquired equivalence learning in healthy participants. The response latencies did not differ significantly between the visual and multisensory paradigms in the acquisition phase. The interpretation of results could that this phase is a very old, conserved and obligatory function, for which the different modalities contribute equally during association learning processes and do not greater efficiency with multisensory stimuli. This is in agreement with the previous studies, which found the activation of the basal ganglia is enhanced at the appearance of rare stimulus associations, which is not influenced by modality (Amso et al., 2005). It cannot be ruled out that the semantic content of the stimuli could affect the learning process. Steinweg and colleagues (2017) found that semantically congruent audiovisual multisensory stimuli support multisensory integration (Steinweg & Mast, 2017). In this study we ignored the semantic contents because the task was making associations regardless of the meaning of the stimuli. In this study we applied stimuli which were mostly semantically incongruent, which could be an interpretation for the lack of multisensory integration in the acquisition phase. In contrast to healthy adults the multisensory information could facilitate the equivalence learning in childhood

(Eördegh et al., 2022). The explanation of it can be that the maximum performances were reached with the application of the audiovisual information in childhood and after it, there is no more chance to improve the performances even by the multimodal stimuli with the aging of the humans.

The second phase of the learning paradigm is the test phase, where the previously learnt acquisitions have to be recalled (retrieval) and new, unknown pairs have to be built (generalization) based on the regularities of associations. These results showed that the audiovisual performances were better but they (RER, GER) were not significantly different in the two (visual vs audiovisual) paradigms. On the other hand, the multisensory response latencies were significantly shorter than the visual ones in both the retrieval and the generalization parts of the test phase. The biggest difference in the response latencies were in the retrieval part of the test phase. If we compare the different phases of the paradigm, we can conclude that the generalization part of the test phase required the longest reaction times irrespective of the stimulus modality. This long decision time confirms that this is the most difficult part of the cognitive learning task. The multisensory information and the connected multisensory integration could improve the performances of the participants in the retrieval and generalization functions, which can obviously be observed in the significant shorter reaction times in the audiovisual paradigm.

6. Summary

Associative learning is a type of conditioning in which discrete and often different signals are linked together. A specific kind of this learning, the sensory guided associative equivalence learning was investigated in the present PhD dissertation. The original Rutgers Acquired Equivalence Test (RAET) examines the visual associative learning and the audiovisual test (SoundFace) investigates the multisensory-guided equivalence learning. Both tests (RAET and SoundFace) have the same structure only the stimuli are unimodal visual or audiovisual. The tests, irrespectively from the modalities can be divided in two main phases: the first is the acquisition phase, which depends critically from the basal ganglia, the second is the test phase (retrieval and generalization), which is connected primarily to the hippocampi.

In the RAET we have investigated the learning functions of 23 borderline personality disorder (BPD) patients and 23 age-, sex-, and educational level-matched controls. In the acquisition phase of the test, the performances were significantly weaker in BPD patients. These results support the notion that the basal ganglia are involved in the pathogenesis of BPD. In contrast, the retrieval and the generalization parts of the test phase were not influenced in BPD patients. The maintenance of retrieval and generalization (transfer) functions could indicate normal hippocampal functions in these patients and could suggest the compensatory role of the hippocampi after a weaker acquisition building.

As described above, both fundamentally-involved brain structures in the visual associative learning, the basal ganglia and the hippocampi, get not only visual, but also multisensory information. Having realized, though, that we did not have normative data about the modality-dependence of the equivalence learning we have developed and validated the audiovisual-guided (multisensory) equivalence learning paradigms in order to compare the performance of healthy volunteers in visual and audiovisual (multisensory) tasks. We compared the learning performance of 151 healthy, adult participants in the visual and the multisensory paradigms. Our results showed that visual and multisensory guided associative equivalence learning is similarly effective in healthy participants, which support that the acquisition phase is fairly independent from the modality of the stimuli. However, in the retrieval and the generalization parts

of the test phase the multisensory stimuli could facilitate the learning, which can obviously be observed in the significant shorter reaction times in the audiovisual paradigm. After the validation of the multisensory test in healthy humans we have now a new tool to investigate the cognitive alterations in different neurological and psychiatric diseases connected to the dysfunction of the basal ganglia and the hippocampi.

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Research article

Visually guided equivalence learning in borderline personality disorder

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ABSTRACT

The hallmark symptoms of borderline personality disorder are maladaptive behavior and impulsive emotional reactions. However, the condition is occasionally associated with cognitive alterations. Recently, it has been found that the function of the basal ganglia and the hippocampi might also be affected. Hence, deterioration in learning and memory processes associated with these structures is expected. Thus, we sought to investigate visually guided associative learning, a type of conditioning associated with the basal ganglia and the hippocampi, in patients suffering from borderline personality disorder. In this study, the modified Rutgers Acquired Equivalence Test was used to assess associative learning in 23 patients and age-, sex-, and educational level-matched controls. The acquisition phase of the test, which is associated primarily with the frontostriatal loops, was altered in patients with borderline personality disorder: the patients exhibited poor performance in terms of building associations. However, the retrieval and generalization functions, which are primarily associated with the hippocampi and the medial temporal lobes, were not affected. These results corroborate that the basal ganglia are affected in borderline personality disorder. However, maintained retrieval and generalization do not support the assumption that the hippocampi are affected too.

1. Introduction

Borderline personality disorder (BPD) is a mental health disorder characterized by maladaptive behavior (long-term pattern of unstable interpersonal relationships and distorted sense of self) and impulsive emotional reactions. Its prevalence rate is 2–3% in the adult population, making it is the most common personality disorder [1]. The disorder usually begins during young adulthood and it has a significantly higher prevalence in women than in men [2].

The neural correlates of BPD have not been fully elucidated. Based on neuroimaging studies, the basal ganglia, the orbitofrontal cortex, the amygdalae, and probably the hippocampi are affected [3, 4, 5, 6, 7]. Due to dysfunction of these brain structures, patients with borderline personality disorder may exhibit altered cognition as compared to persons free of the disorder [8, 9, 10]. However, no information is available about the associative learning abilities of these patients.

Associative learning is an ancient learning function, which is associated with the function of the frontal cortex, the basal ganglia and the hippocampi. The visually guided Rutgers Acquired Equivalence Test [11] assesses this specific type of learning. The test is divided into two main phases: the acquisition phase and the test phase. The acquisition phase relies on the function of the basal ganglia. Hence, association building between two different visual stimuli with the help of feedback about the correctness of responses can be evaluated. Meanwhile, the test phase, which does not involve feedback, mainly depends on the function of the hippocampi and the medial temporal lobe. The test phase is further divided into two parts: retrieval and generalization. During the retrieval part, previously learned associations are presented, while during the generalization part, the task of the test subject is to make hitherto not learned associations which are predictable from what has already been learned.

Equivalence learning was investigated in several psychiatric and neurological disorders, including Parkinson's disease, Alzheimer's disease, schizophrenia, obsessive compulsive disorder, and migraine without aura. These conditions are characterized by the dysfunction of the basal ganglia and hippocampi [11, 12, 13, 14, 15, 16]. As mentioned before, these structures are thought to be dysfunctional in BPD too [11, 12, 13, 14, 15, 16]. However, it is not known whether this also shows in

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the related cognitive processes of BPD patients, such as associative learning. This is what we sought to investigate in this study with the Rutgers Acquired Equivalence Test. As the literature considers both the basal ganglia and the hippocampi to be affected in BPD, we hypothesized that our patients would underperform matched controls in both the acquisition and test phases.

2. Results

In the present study, we analyzed the associative learning abilities of BPD patients without otological, opthalmological, neurological, or psychiatric comorbidities (n = 23). All participants could complete the applied Rutgers Acquired Equivalence Test.

2.1. Comparison of BPD patients and controls

In the acquisition phase of the paradigm, the patient group's performance was significantly inferior to that of the control group (Figure 1).

The median NATs of the patient and control groups were 71.0 (range: 45.0–185.0) and 50.0 (range: 42.0–95.0), respectively (Mann–Whitney U test = 146.5, p = 0.0098, effect size = 0.8077, power = 0.9525). The median ALERs were 0.084 (range: 0.0–0.227) and 0.043 (range: 0.0–0.15) for the patients and controls, respectively (Mann–Whitney U test = 162.5, p = 0.0255, effect size = 0.7845, power = 0.9520). The reaction times of the two groups in the acquisition phase did not differ. The median reaction times were 1565.44 (range: 1034.97–3402.02) ms and 1674.51 (range: 1069.54–3489.21) ms for the patients and controls, respectively (Mann–Whitney U test = 256, p = 0.860).

In the test phase of the paradigm, the performance of the patients and controls did not differ significantly, either in terms of retrieval or generalization (Figure 2).

The median RERs were 0.028 (range: 0.0–0.25) for the patient and 0.028 (0.0–0.22) for the control group (Mann–Whitney U test = 216, p = 0.275). The median GERs were 0.00 (range: 0.0–1.0) and 0.083 (range: 0.0–1.0) for the patient and control groups, respectively (Mann–Whitney U test = 220, p = 0.307). The reaction times of the two groups in the retrieval and generalization parts did not differ. During the retrieval part of the test phase, the median reaction times of the patient and control groups were 1934.37 (range: 1106.66–3728.59) ms and 1693.50 (range: 1145.46–2838.23) ms, respectively (Mann–Whitney U test = 258, p = 0.895). In the generalization part, the median reaction times were 2213.21 (range: 1223.82–8549.00) ms for the patient group and 2309.68 (range: 1158.50–10883.36) ms for the control group (Mann–Whitney U test = 235, p = 0.879).

In the patient group, we also calculated the correlation (Pearson's r) between test performance and the time elapsed since the diagnosis. At the time of testing, the patients had been diagnosed with BPD for a mean of 12.9 years (±9.9 years). None of the investigated parameters (NAT, ALER, RER, GER and RTs) showed significant correlation with the time elapsed since the diagnosis (p > 0.05).

2.2. Performance of BPD patients according to medication status

In the acquisition phase of the paradigm, the performance of the medicated subgroup did not differ from that of the non-medicated subgroup. The median NATs of the medicated and non-medicated subgroups were 69.0 (range: 45.0–133.0) and 80.0 (range: 46.0–185.0), respectively (Mann–Whitney U test = 47, p = 0.4196). The median ALERs were 0.077 (range: 0.0–0.218) for the medicated subgroup and 0.117 (range: 0.043–0.227) for the non-medicated subgroup (Mann–Whitney U test = 36, p = 0.129).

Medication status did not make a significant difference in the test phase either. The median RERs were 0.028 (range: 0.0–0.167) for the medicated subgroup and 0.056 (range: 0.0–0.250) for the non-medicated subgroup (Mann–Whitney U test = 48.5, p = 0.468). The median GERs were 0.00 (range: 0.0–1.0) and 0.00 (range: 0.0–0.750) for the medicated and non-medicated subgroups, respectively (Mann–Whitney U test = 56.5, p = 0.830).

3. Discussion

To our knowledge, this study has been the first to investigate the visually guided associative learning abilities of BPD patients. The results suggest that BPD patients experience difficulties with equivalence learning (making pairs by association), but not with the retrieval of already learned associations or even making inferences from them regarding previously not learned associations.

The results of studies about the impairment of implicit and explicit learning functions in BPD patients are controversial. Earlier studies found no alterations in implicit statistical learning [17] and procedural memory consolidation in patients with BPD [18]. However, primary implicit acquired equivalence learning, which is mainly correlated with the function of the basal ganglia, was found to be significantly altered in the BPD group of our study. Similarly, a comprehensive clinical and neuropsychological study revealed deficits in this patient group in visually guided functions such as visual memory, visuospatial abilities, and executive functions [19]. In contrast, the psychophysical part of a functional magnetic resonance imaging (fMRI) study found no significant difference in visually guided episodic and semantic memory retrieval between BPD patients and controls. However, a stronger cortical activation was required for the same performance in the patient group [20]. Verbal and visual episodic memory appear to be spared in BPD [21], but these patients exhibit poor performance in the go/no-go task, which indicates response inhibition impairment [22].

In the current study, we applied the modified version [14] of the original Rutgers Acquired Equivalence Test [11, 23]. The test was developed to investigate the visually guided associative learning in healthy humans and those with various psychiatric and neurological disorders. Its acquisition phase tests association learning between two independent visual stimuli, which is considered to depend on the intact function of the basal ganglia [11, 23]. Therefore, this phase is assumed to

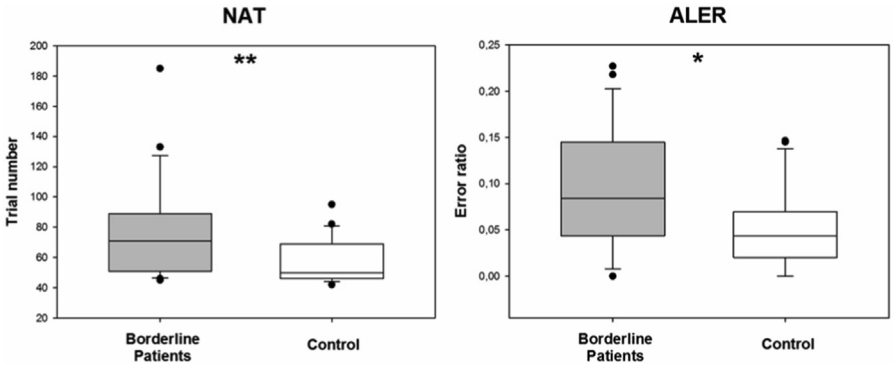

Figure 1. Performance in the acquisition phase. NAT: the number of trials necessary for the completion of the acquisition phase. ALER: the ratio of incorrect choices during the acquisition trials. The lower margin of the boxes represents the 25th percentile. The line within the boxes marks the median, and the upper margin of the boxes indicates the 75th percentile. The error bars (whiskers) above and below the boxes denote the 90th and 10th percentiles, respectively. The dots over and under the whiskers indicate the extreme outliers. *: p < 0.05, **: p < 0.01.

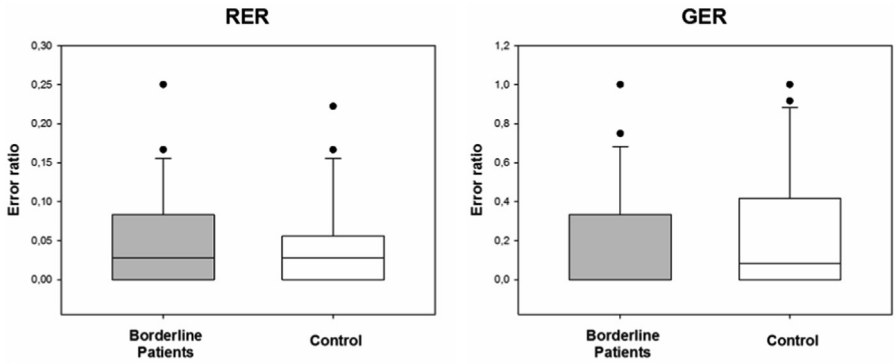

Figure 2. Performance in the test phase. RER: error ratios in the retrieval phase. GER: error ratios in the generalization phase. The conventions are the same as in Figure 1.

test the adequate functioning of the basal ganglia. Accordingly, poor performance has been reported in Parkinson's disease [11], Tourette syndrome [24], and adult migraine [14]. The test phase focuses on functions that are assumed to be mediated by the hippocampi and the medial temporal lobes: retrieval and generalization based on the retrieved information [23, 25]. Poor performance in the test phase has been reported in hippocampus–medial temporal lobe injury [23, 26], Alzheimer's disease [12], and adult migraine [14].

In this study, we have described the cognitive performance of a group of BPD patients without any neurological and/or psychiatric comorbidity (including substance abuse), as assessed by the Rutgers Acquired Equivalence Test.

The results of the acquisition phase (NAT, ALER) indicate that BPD patients found it more difficult to build associations between independent visual stimulus pairs. This finding may be interpreted as a behavioral indicator of suboptimal basal ganglia function in BPD, and so it corroborates the results of studies that suggest that the basal ganglia are affected in this personality disorder [6, 7, 8, 9].

A comparison of reaction times did not reveal differences between patients and controls, which suggests that the difference found in the acquisition phase did not stem from impaired response inhibition in the patient group (which would be indicated by significantly shorter reaction times). This is not necessarily evidence against the presence of impaired response inhibition in this patient population as suggested by Rentrop and colleagues [23], but even if it is a stable feature of BPD patients, it did not influence their performance in this task.

In contrast to the acquisition phase, however, no significant difference was found between patients and controls in the test phase. That is, BPD patients retrieved the previously learned associations and generalized the previously acquired rule of association to new stimulus pairs just as efficiently as controls. In fact, the generalization performance of BPD patients was slightly superior to that of controls, which raises the possibility that in BPD and in this specific task, the hippocampi may function somewhat more efficiently. While the difference was not significant, and we definitely do not have enough data to draw a firm conclusion regarding this issue, it must be noted that such a compensatory function of the hippocampi has been reported in other studies regarding learning [27, 28]. Therefore, as this phase of the test is assumed to depend on the hippocampi, the results may be interpreted as evidence against the hippocampi being affected in BPD - at least, if there is hippocampal involvement, it does not interfere with retrieval and generalization in the context of equivalence learning.

We also considered some potential limitations when interpreting the results of this study. The first one is the relatively low number of participants. This, however, is only a prima facie limitation and we argue that it did not interfere with the generalizability of the results. On one hand, this low number of participants was the result of the strict application of the diagnostic criteria and that substance abuse and neurological/psychiatric comorbidity were exclusion criteria. This way, it became possible to focus on the effect of BPD itself. On the other hand, the statistical tests that returned significant results had a high statistical power (and also a large effect size) so, in this case, a seemingly small sample size did not result in poor statistical power. All in all, the small size of the sample in itself cannot put the validity and generalizability of our results in question.

Another concern was that medications might affect the performance of BPD patients. In an attempt to exclude this possibility, we compared the performance of medicated and non-medicated patients. No difference was found between these subgroups in any of the studied parameters. However, it must be added that splitting the patient group into two subgroups resulted in quite small subsamples, so we advise against interpreting this result as evidence for the complete absence of such an effect.

4. Materials and methods

4.1. Participants

In total, 23 patients with borderline personality disorder (18 women and 5 men, mean age: 28.9 ± 9.6 [range: 18–55] years, median education level: 3.0 [range: 1.0–4.0]) were enrolled in this study. The educational levels were as follows: 1–elementary school, 2–secondary school, 3–high school, 4–university. Inpatients and outpatients from the Department of Psychiatry (Faculty of Medicine, University of Szeged) were recruited. The patients were diagnosed by psychiatrists at the hospital according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition [2]. All patients were diagnosed with borderline personality disorder. Patients with otological, ophthalmological, neurological, or psychiatric comorbidities (including substance abuse) were not eligible for the study. In total, 15 patients received medications (see below). From our database, 23 matched healthy controls (18 women and five men, mean age: 28.7 ± 9.2 [range: 18–53] years, median education level: 3.0 [range: 2.0–4.0]) were identified and individually matched to the patients based on sex, age (difference $\leq$2 years), and education level. The comparison of the demographic data revealed no differences between the patient and control groups (Kruskal–Wallis test, $p > 0.05$) (Table 1).

Prior to testing, the Ishihara plates were used to rule out color blindness in both groups. Only subjects with normal color vision were included in the study.

None of the participants received financial compensation for their participation, and all patients provided written informed consent prior to the start of the study. This research was performed in accordance with the tenets of the Declaration of Helsinki, and it was approved by the Regional Ethics Committee for Medical Research at the University of Szeged, Hungary (50/2015-SZTE).

Fifteen of the 23 patients received several types of medication. Seven of the fifteen patients received monotherapy as follows: two patients received H1 antihistamine (hiroxizine), three patients received either of

Table 1. Demographic data of the patients and controls.

Group	Number of cases	Female/male	Age, mean (years)	Age, range: (years)	Educational level median (range)
All patients	23	18/5	28.9 ± 9.6	18–55	3.0 (1.0–4.0)
All controls	23	18/5	28.7 ± 9.2	18–53	3.0 (2.0–4.0)
Medicated patients	15	12/3	31.2 ± 10.7	18–55	3.0 (1.0–4.0)
Controls matched to medicated patients	15	11/4	30.7 ± 10.1	18–53	3.0 (2.0–4.0)
Unmedicated patients	8	6/2	24.6 ± 5.4	18–34	3.0 (3.0–4.0)
Controls matched to unmedicated patients	8	7/1	24.9 ± 5.6	18–35	3.5 (3.0–4.0)

three serotonergic medications (escitalopram, fluoxetine, vortioxetine) and two patients received antipsychotics (olanzapine, aripiprazole). Further five of the fifteen patients received a combination of two agents: two of them received the combination of an SSNRI (venlafaxine) and a GABA agonist (benzodiazepine or alprazolam); one of them received a combination of two types of GABA agonists (benzodiazepine and imidazopiridine); one of them received a combination of a GABA agonist (alprazolam) and a mood stabilizer (lamotrigine); and one of them received the combination of an SSRI (escitalopram) and an atypical antipsychotic (quetiapine). Finally, three of the fifteen medicated patients received three agents in combination: a GABA agonist (benzodiazepine, imidazopiridine or alprazolam), an SSNRI (duloxetine or venlafaxine) and a third agent, which was either a melatonine receptor agonist (agomelatine) or an atypical antipsychotic (olanzapine).

At the time of testing, the patients have taken their medications for a mean of 9.21 (±6.29) years (median: 9 years, range: 1–20 years, lower quartile: 4 years, upper quartile: 14 years).

4.2. The learning paradigm

Testing was carried out according to Myers and co-workers, according to the method known as the Rutgers Acquired Equivalence Test [11]. The testing software, which was originally prepared for iOS was rewritten in Assembly (for Windows). Stimuli were presented and responses were recorded with a desktop computer with a CRT screen. The testing sessions took place in a quiet room with the subjects sitting at a standard distance from the computer screen (114 cm). One subject was tested at a time and no time limit was set. Figure 3 shows a schematic representation of the paradigm.

The visual stimuli referred to as antecedents were cartoon faces of a woman (A1), a girl (A2), a man (B1) and a boy (B2). The consequents were yellow (X1), red (X2), green (Y1) and blue (Y2) fish.

During a trial, the participant was shown an antecedent (a face) and two consequents (a pair of fish of different color) and asked to choose one of the latter by pressing one of two buttons on the keyboard marked as

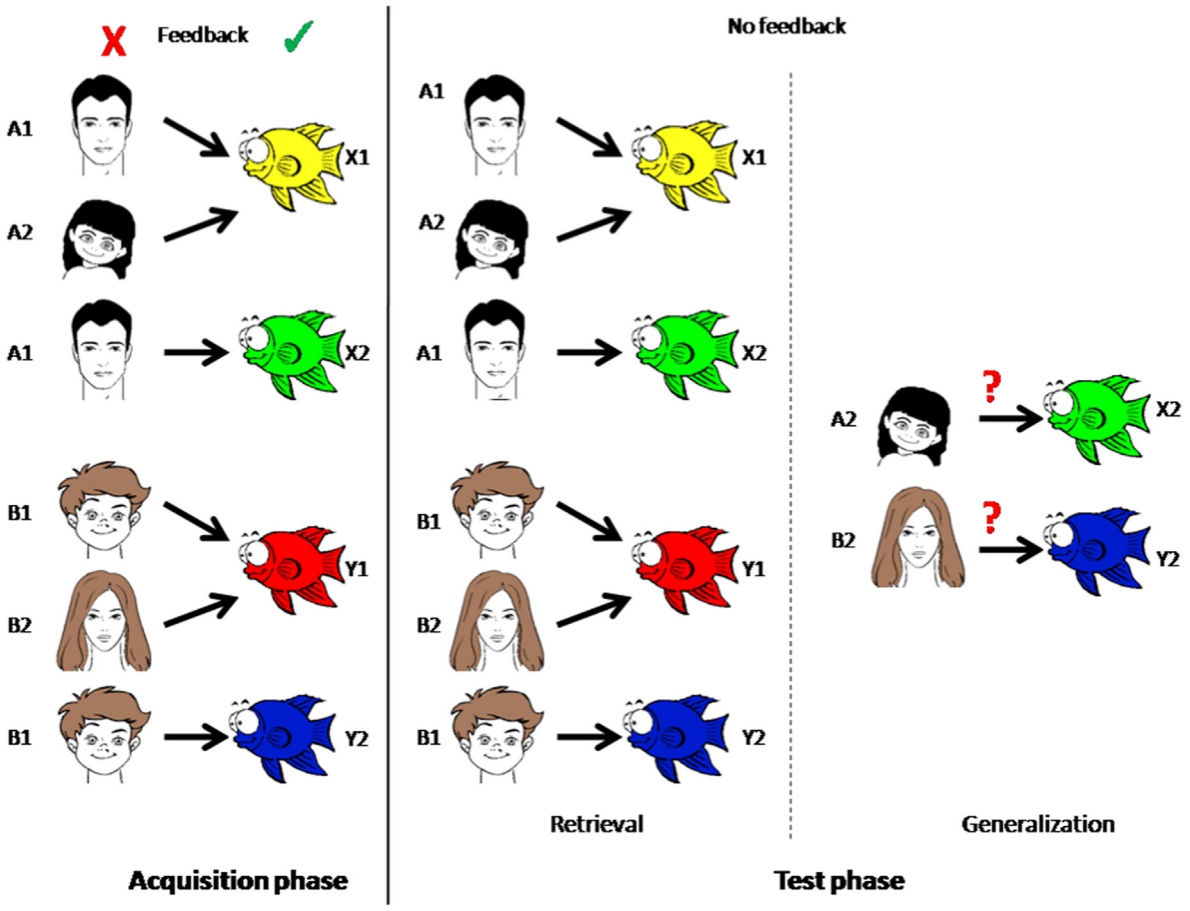

Figure 3. A schematic representation of the applied visually guided associative learning paradigm.

LEFT and RIGHT. The trials are organized into two main phases: acquisition and test. The test phase is further broken down to retrieval and generalization (see below). Depending on the phase the participant was in, the choice was (acquisition phase) or was not (test phase) followed by feedback on the correctness of the choice.

During the acquisition phase, the participants learned a series of antecedent-consequent pairs in a trial-and-error manner. When antecedents A1 or A2 were shown, the correct consequent was X1. On the other hand, when antecedent B1 or B2 were presented, the correct consequent was Y1. Visual feedback on the correctness of the subject's choice was provided immediately in the form of the words CORRECT (in green) and INCORRECT (in red) displayed on the screen under the antecedent-consequent pair. This way, besides the face-fish associations, the participants also learned that the antecedent A1 (B1) is equivalent to antecedent A2 (B2) in terms of their relation to the same consequent. Next, the participants had to learn new stimulus pairs. In case of antecedents A1 and B1, the correct consequents were X2 and Y2, respectively. Of the eight possible stimulus combinations, six were presented in the acquisition phase of the equivalence learning task. New association were presented mixed with the previously learned ones. The subjects had to accomplish a certain number of correct decisions, 4 when the first association was presented, and it was increased by 2 upon the presentation of each new association that followed up to a maximum of 12. Thus, the number of trials in the acquisition phase was not constant, it depended on the effectiveness of the learning of the participants.

In the test phase, the task remained the same, but visual feedback was no longer given. During the retrieval part of the test phase the already learnt six stimulus pairs were tested. In the generalization (or transfer) part of the test phase, hitherto not presented, new stimulus pairs were also tested. These were predictable if the participant had managed to acquire the equivalence rule (antecedent A1 and A2 are equivalent upon the connected consequences, similarly B1 and B2, too). Here the participants had to choose that antecedent A2 and B2 were coupled to consequences X2 and Y2, respectively. Participants were not informed that new associations would have to be formed, too. These new stimulus pairs were mixed with the earlier ones. The number of trials in the test phase was constant for each participant. Altogether 48 trials (36 previously learned and 12 new, predictable associations) had to be completed in the test phase.

More detailed description of the paradigm can be found in our previous studies [29, 30].

4.3. Data analysis

The performance of the participants was characterized with four main parameters: the number of trials necessary for the completion of the acquisition phase (NAT), association learning error ratio (ALER), retrieval error ratio (RER), and generalization error ratio (GER). Error ratios were calculated by dividing the number of incorrect trials by the total number of trials. Reaction times were recorded for the acquisition phase, the retrieval part of the test phase and the generalization part of the test phase.

After having determined that the data were non-normally distributed (Shapiro-Wilk $p < 0.05$), comparisons between BPD patients and controls were performed with the Mann-Whitney U test. The level of significance was set at $p = 0.05$. For the descriptive characterization of the data, medians and ranges were used.

Declarations

Author contribution statement

Anett Rosu; Kálmán Tót: Performed the experiments; Analyzed and interpreted the data; Wrote the paper.

György Godó: Performed the experiments; Analyzed and interpreted the data.

Szabolcs Kéri: Conceived and designed the experiments; Contributed reagents, materials, analysis tools or data.

Attila Nagy: Conceived and designed the experiments; Contributed reagents, materials, analysis tools or data; Wrote the paper.

Gabriella Eördegh: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Wrote the paper.

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Data availability statement

Data will be made available on request.

Declaration of interests statement

The authors declare no conflict of interest.

Additional information

No additional information is available for this paper.

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RESEARCH ARTICLE

Multisensory guided associative learning in healthy humans

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Abstract

Associative learning is a basic cognitive function by which discrete and often different percepts are linked together. The Rutgers Acquired Equivalence Test investigates a specific kind of associative learning, visually guided equivalence learning. The test consists of an acquisition (pair learning) and a test (rule transfer) phase, which are associated primarily with the function of the basal ganglia and the hippocampi, respectively. Earlier studies described that both fundamentally-involved brain structures in the visual associative learning, the basal ganglia and the hippocampi, receive not only visual but also multisensory information. However, no study has investigated whether there is a priority for multisensory guided equivalence learning compared to unimodal ones. Thus we had no data about the modality-dependence or independence of the equivalence learning. In the present study, we have therefore introduced the auditory- and multisensory (audiovisual)-guided equivalence learning paradigms and investigated the performance of 151 healthy volunteers in the visual as well as in the auditory and multisensory paradigms. Our results indicated that visual, auditory and multisensory guided associative learning is similarly effective in healthy humans, which suggest that the acquisition phase is fairly independent from the modality of the stimuli. On the other hand, in the test phase, where participants were presented with acquisitions that were learned earlier and associations that were until then not seen or heard but predictable, the multisensory stimuli elicited the best performance. The test phase, especially its generalization part, seems to be a harder cognitive task, where the multisensory information processing could improve the performance of the participants.

Introduction

Associative learning is a basic cognitive function by which discrete and often different percepts will be linked together. It contributes to several cognitive tasks, i.e. classical conditioning [1], latent inhibition [2] and sensory preconditioning [3]. Catherine E. Myers and co-workers developed a learning paradigm (Rutgers Acquired Equivalence Test, also known as the fish-

face paradigm) that can be applied to investigate a specific kind of associative learning, which is visually guided equivalence learning [4]. This test can be divided into two main phases. In the acquisition phase, the subjects are asked to associate two different visual stimuli as the computer provides information about the correctness of the responses. After that in the test phase the subjects receive no feedback about the correctness of their choices. In the test phase, beside the stimulus pairs learned earlier (retrieval part), hitherto not encountered but predictable associations (generalization part) are also presented. A substantial advantage of this test is that well-circumscribed brain structures play the main role in different phases of the test. Optimal performance in the acquisition phase appears to depend mainly on the integrity of the basal ganglia, whereas performance in the test phase (both retrieval and generalization) has been linked to the integrity of the hippocampal region [4, 5]. Our research group has a particular interest in the sensorimotor and cognitive functions of the basal ganglia and has studied with this paradigm since 2006, mostly to assess the development of visually guided associative learning [6] and to examine the progress in various conditions, from Alzheimer's disease to migraines [7–9]. It is well known from earlier studies that both brain structures fundamentally involved in visual associative learning, the basal ganglia and the hippocampi, receive not only visual but also multisensory information [10–13]. Multimodal information could be more informative than a unimodal stimulus from the environment [14, 15]. Probably because of the merging of senses, multisensority has a priority in spatial orientation and in recognizing objects and events from the multisensory environment [14–16]. Multisensory integration occurs at different levels of brain functions. It can be observed at the cellular level [17–20] in several brain regions such as the superior colliculus [21], basal ganglia [11, 22] the cortex [23], and the hippocampus [24] or on the behavioral level [25, 26]. It can occur between two or three different modalities, for example auditory and visual [27, 28], visual and vestibular [29], auditory and tactile [30], or auditory, visual and somatosensory [11, 31, 32].

Having realized, though, that we did not have normative data about the modality-dependence of equivalence learning, we aimed to develop and introduce the auditory-guided and multisensory (audiovisual)-guided equivalence learning paradigms in order to compare the performance of healthy volunteers in the three (visual, auditory and multisensory) tasks. Special attention was paid to whether, during multisensory-guided learning, the earlier-described multisensory integration can be found on the behavioral level during multisensory-guided acquired equivalence learning. Earlier studies denoted that the multisensory information could facilitate learning. Multisensory information increases the learning speed in discrimination learning [33]. This occurs in selective learning tasks, too [34]. It is also known that the spatially coupled different modality stimuli could elicit more accurate orientation behavior than the spatially separated ones [35, 36]. We asked in the present study whether multisensory stimuli could similarly facilitate the acquired equivalence learning at a behavioral level. The general hypothesis of the present study was that multisensory guided associative learning is more effective in both its acquisition and test phases compared to those that employ unimodal visual and auditory guided paradigms.

Methods

Subjects

Altogether 151 healthy adult volunteers were involved in the research. All subjects were Caucasian. Only persons free of any ophthalmological, otological, neurological and psychiatric conditions were eligible. Intactness of color vision was tested by Ishihara plates prior to testing to exclude color blindness [37]. The potential subjects were informed about the background and goals of the study, as well as about the procedures involved. It was also emphasized that, given

the lack of compensation or any direct benefit, the participants were free to quit at any time without any consequence (no one did so). Each participant 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 on several occasions by the Regional Research Ethics Committee for Medical Research at the University of Szeged, Hungary (50/2015-SZTE).

The sensory guided associative learning paradigms

The tests were run on laptop computers (Lenovo T430, Fujitsu Siemens Amilo Pro V3505, Samsung Electronics 300e4z/300e5z/300e7z, Lenovo Yoga Y500) and with Sennheiser HD 439 closed, over-ear headphones for auditory and multisensory testing. The testing sessions took place in a quiet room with the subjects sitting at a standard distance (114 cm) from the computer screen. The M and X keys of the laptop keyboards were labeled left and right, respectively. One subject was tested at a time, and no time limit was set, so the subject could pay involuntary, undivided attention to learning. No forced quick responses were expected. The original visual associative learning test [4] written for iOS was slightly modified, translated to Hungarian and rewritten in Assembly (for Windows) with the written permission of Prof Catherine E. Myers (Rutgers University, NJ, USA), the corresponding author of the above-mentioned paper [4]. Beside the visually guided test, we also introduced an auditory and a multisensory (audiovisual) guided learning test, implemented in Assembly (for Windows). During the tests the participants had to associate two kinds of information referred to as antecedents and consequents. The participants were asked to learn associations of antecedent and consequent stimuli through trial and error during the task, and indicate their choice by pressing either the LEFT or RIGHT button of the laptop keyboard. The left or right button corresponded to the picture on each side of the computer monitor. All three paradigms were tested in two main phases, the acquisition and the test phases. In the acquisition phase the participant had to form associations between definite stimuli (equivalence acquisition) and the computer gave feedback about the success of the acquisition. A green check mark appeared on the screen to indicate a correct answer, while an incorrect answer was indicated by a red X. New associations were introduced one by one during the acquisition phase. The test phase, where no further feedback was provided, can be divided into two parts. Here the participant had to recall the previously-learned associations (in the retrieval part) and had to build new, hitherto-unknown but predictable acquisitions (in the generalization part) based on the rules learned in the acquisition phase. In the test phase the unknown new associations were presented mixed among the previously-learned ones. 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 ensured that the participants proceeded to the test phase only when they had memorized all the associations shown in the acquisition phase. Thus there were not a constant number of trials in the acquisition phase; the number depended on the performance of the subjects. On the other hand, the test phase consistently contained 48 trials, 36 of them previously-learned associations (retrieval part) and 12 new, previously not presented but predictable associations (generalization part).

Visual paradigm. Fig 1 illustrates the task in the three different paradigms.

The principle of the visual paradigm (Fig 1, top) is based on the Rutgers Acquired Equivalence Test (RAET) of Myers et al [4]. During each trial of the task the participants saw a face and a pair of fish, and were asked to choose which fish is matched with the given face. The faces were a girl, a boy, a man and a woman. The fish, which were of the same shape, had different colors: green, red, yellow and blue. There were four faces (A1, A2, B1, B2) and four fish

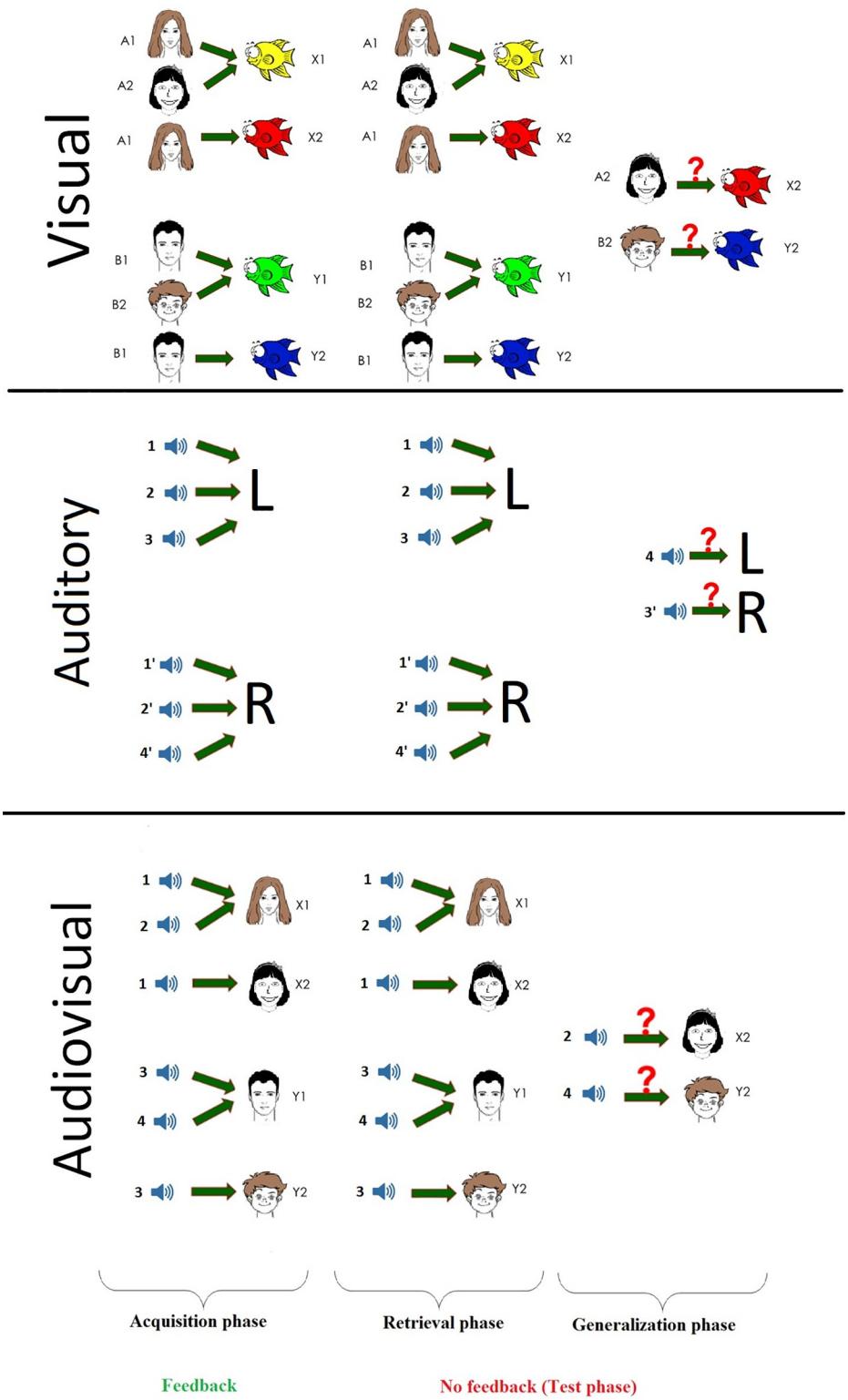

Fig 1. The schematic drawing of the applied visual, auditory and multisensory guided associative learning paradigms. See details in text.

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(X1, X2, Y1, Y2) which could build eight pairs altogether. During the first two parts of the acquisition phase, the participants were expected to learn that when face A1 or A2 appeared, the correct answer was to choose fish X1 over fish Y1; given face B1 or B2, the correct answer was to choose fish Y1 over fish X1. This way the participants also learned that face A1 and A2 were equivalent in their consequent (face B1 and B2 likewise). In the next stage new consequents (X2, Y2) were introduced. Given face A1, participants had to choose fish X2 over Y2, and given face B1 they had to choose fish Y2 over X2. Until this point, participants had received feedback about the correctness of the decision. In the test phase, without any further feedback, the test presented the two new combinations beside the already-learned acquisitions. If the participants learned that A1 and A2 are equivalent, similarly to B1 and B2, they could generalize the previously-learned rule and could associate fish X2 with face A2 to (the fish that was associated with A1) and fish Y2 with face B2 to (the fish that was associated with face B1).

Auditory paradigm. In the auditory task the participants had to learn to associate sounds (antecedents) with the left or right buttons (L or R as consequents in Fig 1 middle), similarly to the visual paradigm, 8 pairs were built. Eight different sounds distributed into four pairs were used (in Fig 1 the following four sound pairs can be seen: sound 1 and sound 1', sound 2 and sound 2', sound 3 and sound 3', sound 4 and sound 4'): two human voices of different genders (who said a word in Hungarian with neutral emotional tone), two animal sounds (a cat meowing, a dog barking), two sounds of musical instruments (a guitar, a piano), and two vehicle sounds (a motorcycle, an ignition key). The different sounds were randomly presented to each participant, so for example in one case, the sound 1 and sound 1' mean the two animal sounds, in another case the sound 1 and sound 1' mean the two vehicle sounds, etc. Each sound was 1.5 s long, and had the same intensity (SPL = 60 dB). The sound clips were played to the participants before the testing began through the headphones to each ear. The grouping was reflected in the distribution of sounds between the buttons: the first sound of a pair could be associated with to one key and the second sound of the same pair to the other key. The participants were expected to learn the pattern through trial and error, and apply it in the generalization phase of the task. During the acquisition phase the participants learned to associate two pairs of sound with buttons (altogether four associations), thus learning the pattern. Then the associations of one sound from each of the two remaining groups were learned. In the test phase, the participants had to generalize the correct association of the remaining two sounds. For feasibility reasons, which will be discussed in detail in the Discussion part of the paper, the auditory guided task does not totally correspond to the visual and multisensory guided ones. Although all of the learning tasks contain eight stimuli, in the auditory paradigm, in contrast to the visual and multisensory test where two visual or an auditory and a visual stimuli had to be associated, the sound has to be associated not with a second sound but with a particular button.

Multisensory paradigm. Apart from the stimuli, the experimental procedure of the multisensory (audiovisual) paradigm was exactly the same as the visual paradigm (Fig 1, bottom). Clearly-distinguishable sounds (one of the antecedents pairs used in the auditory paradigm: a cat's meow, the sound of an ignition key, a note played by a guitar and a woman saying a Hungarian word with neutral emotional tone) served as antecedents (sound 1, sound 2, sound 3, sound 4) and faces were used as consequents (X1, X2, Y1, Y2). In each trial a sound (SPL = 60 dB) was played and two faces were presented to the participants, who had to learn which sound goes with which face. The stimuli were presented at the same time on the computer screen and through the headphones. The participants were asked to choose which face (left or right) is coupled with the given sound and were asked to press the corresponding button (left or right) on the keyboard. The auditory and visual components of the multisensory stimulus pairs were primarily semantically incongruent (except in the case of a woman's voice being matched with a woman's face).

Data analysis

The trial numbers, the response accuracy (error ratios) and response times were analyzed in three groups in each paradigm: the acquisition phase, the retrieval part of the test phase and the generalization part of the test phase (minimal data set can be found in S1 File.). We registered the number of trials needed 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. Using these data, the error ratios were calculated: the ratio of the correct 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). Reaction times (RT) in each phase for each answer were measured in ms with μs accuracy. The RTs were kept only within 3SDs of participants' average.

To avoid a carry-over effect between paradigms, the different paradigms were recorded in a random order with each person.

The statistical analysis was performed in Statistica 13 (Dell Inc. USA) and G*Power 3.1.9.2. (Düsseldorf, Germany). One-way ANOVA was applied in order to compare the performances and the response times for each phase of the three learning paradigms. If the ANOVA analysis revealed significant difference among the values, the Tukey HSD post hoc test was applied to check the data pairwise. The effect sizes were calculated from means (in Statistica RMSSE, Root Mean Square Standardized Effect) because of the applied One-way ANOVA method. To determine the validity of the Miller's race model [38, 39] an algorithm, developed earlier by Ulrich et al. [40] was applied on the visual, auditory and audiovisual response latencies in the generalization part of the paradigms.

Results

Altogether 151 healthy volunteers participated in the study. Only a small minority of the participants (7/151) did not complete all three (visual, auditory, multisensory) paradigms. All of the participants could complete the visual paradigm, one of them could not learn the auditory, and six of them could not learn the multisensory associations. Only the performance and RT of those participants who completed all the three paradigms were further analyzed. After the further exclusion of the extreme outliers, 141 volunteers will be analyzed in detail (n_{male} = 41, age: 31.21±11.51 years, range: 18–72 years). The outliers were determined as a value above the mean +3SD (by the trial number in one of the paradigms).

The performance in the three paradigms

The mean of the NAT necessary to learn the visual paradigm was 66.48 (range: 41–269, SEM: ±2.61, n = 141), in the case of the auditory paradigm it was 71.74 (range: 38–292, SEM: ±4.00, n = 141) and in the case of the multisensory paradigm it was 63.82 (range: 41–226, SEM: ±2.41, n = 141). The NATs did not differ significantly among the three (visual, auditory and multisensory) paradigms (ANOVA ($F_{(2, 420)}$ = 1.7097, p = 0.18219) (Fig 2A).

In the visual paradigm the mean of the ALER was 0.0771 (range: 0–0.3333, SEM: ±0.0058), in the auditory paradigm it was 0.0715 (range: 0–0.359, SEM: ±0.0064) and in the multisensory paradigm it was 0.0724 (range: 0–0.347, SEM: ±0.0051). Similarly to the NATs, the ALERs showed no significant variation among the visual, auditory and multisensory paradigms (ANOVA $F_{(2, 420)}$ = 0.26517, p = 0.76721 (Fig 2B)).

In the retrieval part of the test phase the RER was the highest in the auditory paradigm (mean: 0.07348, range: 0–0.4167, SEM: ±0.0075), it was moderate (mean: 0.0581, range:

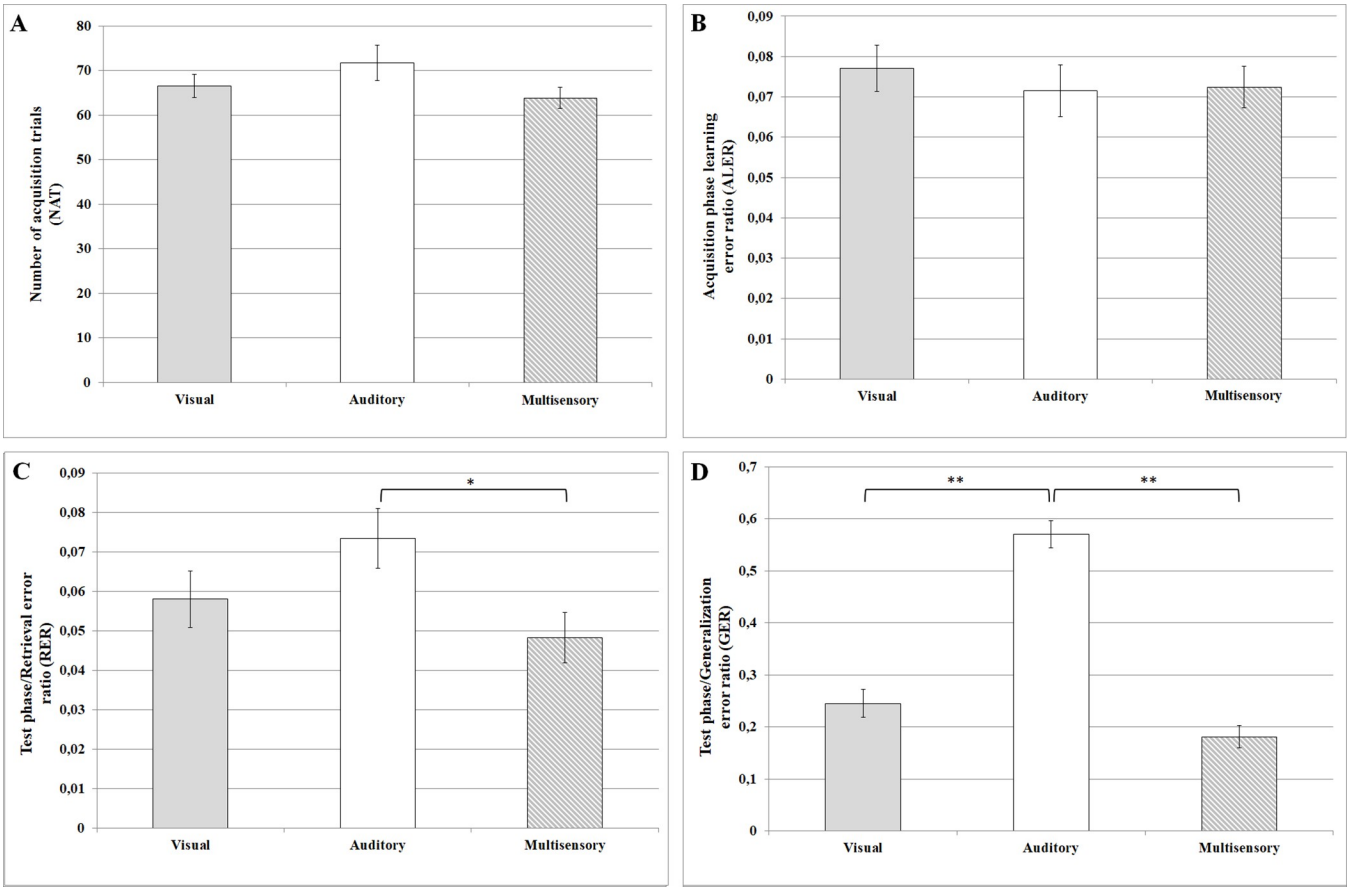

Fig 2. Performances in the sensory guided equivalence learning paradigms. (A) denotes the number of the necessary trials in the acquisition phase of the paradigm. (B) shows the error ratios in the acquisition phase of the paradigm. (C) and (D) denote the error ratios in the retrieval and generalization parts of the test phase, respectively. In each panel, the first column (light grey) shows the results in the visual paradigm, the second column (white) denotes the results in the auditory paradigm and the third column (grey-white striped) demonstrates the results in the multisensory (audiovisual) paradigm. Mean ± SEM values are presented in each column. The black stars denote the significant differences. The single star in part C represents a significant difference, where $p<0.05$; the two stars in part D represent strongly significant differences, where $p<0.001$.

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0–0.4167, SEM: ±0.0072) in the visual paradigm and it was the lowest in the multisensory paradigm (mean: 0.0483, range: 0–0.4167, SEM: ±0.0064). There was a significant difference among these values (ANOVA: $F_{(2, 420)} = 3.2659$, $p = 0.03913$, Effect size: 0.0104, Power: 0.0420). The Tukey HSD post hoc test revealed that the multisensory RER was significantly lower than the auditory one ($p = 0.030191$), but there were no significant differences between the other combinations (Fig 2C).

The same trend can be observed in the generalization part of the test phase among the GERs. The GERs were the highest in the auditory paradigm (mean: 0.5703, range: 0–1, SEM: ±0.0264), while in the visual and multisensory paradigms they were nearly half of the auditory GER (visual mean: 0.2447, range: 0–1, SEM: ±0.0268, multisensory mean: 0.1809, range: 0–1, SEM: ±0.0217). There was a significant difference among these values (ANOVA $F_{(2, 420)} = 9.4153$, $p<0.0001$, Effect size: 0.2089, Power: 0.2444). The Tukey post hoc analysis revealed that both the visual and multisensory GERs were significantly lower than the auditory ones (visual vs. auditory $p<0.001$; multisensory vs. auditory $p<0.001$ (Fig 2D)).

In order to exclude the effect of learning during the tests, we investigated the effect of the sequence of the paradigms on performance. Altogether six different orders of paradigms were

used, as their order was selected at random (Visual (V), Auditory (A), Multisensory (M), VMA, AVM, AMV, MVA, MAV). The statistical analysis (ANOVA) revealed no significant differences among the NATs, ALERs, RERs and GERs in the six possible orders.

Latency of the correct trials in the three paradigms

Fig 3 denotes the mean latencies of the correct trials in the acquisition phase and in the retrieval and generalization parts of the test phase in the three paradigms.

We compared the latency of the correct trials among the same phases of the different paradigms. The mean latency of the auditory correct trials in the acquisition phase was significant shorter (mean: 1447.86 ms, range: 850.43–3208.45 ms, SEM: ±28.92 ms, n = 141), than that of the visual (mean: 1721.21 ms, range: 841.63–3885.76 ms, SEM: ±49.31 ms, n = 141) and multisensory correct trials (mean: 1686.22 ms, range: 894.23–4017.16 ms, SEM: ±40.03 ms, n = 141; ANOVA ($F_{(2, 420)}$ = 13.630, $p<0.001$, Effect size: 0.1218, Power: 0.9586, Tukey HSD post hoc between visual vs. auditory $p<0.001$, multisensory vs. auditory $p<0.001$) (Fig 3A).

Similarly to the acquisition phase, the mean latencies of the correct trials were different in the retrieval part of the test phase (ANOVA $F_{(2, 420)}$ = 9.7615, $p<0.001$, Effect size: 0.105, Power: 0.9522, Tukey HSD post hoc visual vs. auditory $p<0.001$, visual vs. multisensory p = 0.0022). The mean latency of the visual correct trials was significantly longer (mean: 1782.65 ms, range: 825.81–4656.29 ms, SEM: ±55.39 ms, n = 141), than that of the auditory (mean: 1538.68 ms, range: 814.86–2884.62 ms, SEM: ±31.67 ms, n = 141) and multisensory correct trials (mean: 1585.58 ms, range: 893.58–2988.21 ms, SEM: ±32.86 ms, n = 141) (Fig 3B).

The mean latencies of the correct trials in the generalization part of the test phase differed significantly by modality ($F_{(2, 380)}$ = 7.3734, p = 0.00072, Effect size: 0.2527, Power: 0.9503, Tukey HSD post hoc visual vs. auditory p = 0.0306, visual vs. multisensory p = 0.00053). In the generalization part of the test phase the mean latency of the visual correct trials was the longest (mean: 2677.81 ms, range: 940.8–10883.36 ms, SEM: ±145.95 ms, n = 133) and differed significantly from the other two (auditory mean: 2260.82 ms, range: 912.5–7633.5 ms, SEM: ±99.19 ms, n = 113; multisensory mean: 2089.71 ms, range: 882.58–6969.5 ms, SEM: ±84.12 ms, n = 137) (Fig 3C). While the mean multisensory response latency was the shortest in the generalization part of the test phase, the question arises whether this is because of the race between the visual and auditory modalities or because of the multisensory integration. In order to check this issue the race model inequality was analyzed (see S3 Fig). Based on these results the race model inequality can be held, which contradicts the effect of crossmodal multisensory integration on the audiovisual (multisensory) response latencies.

ANOVA analysis and the connected Tukey HSD post hoc analysis revealed that in all visual, auditory and multisensory paradigms the mean latency of the correct trials was significantly longer in the generalization part of the test phase than those in the acquisition phase or the retrieval part of the test phase. (The results of the detailed statistical analysis can be found here: visual paradigm $F_{(2, 412)}$ = 33.19, $p<0.000001$, Effect size: 0.4326, Power: 0.9532, post hoc acquisition vs. generalization p = 0.00002, retrieval vs. generalization p = 0.00002; auditory paradigm $F_{(2, 392)}$ = 58.63, $p<0.000001$ Effect size: 0.349, Power: 0.9532, post hoc acquisition vs. generalization p = 0.00002, retrieval vs. generalization p = 0.00002; multisensory paradigm $F_{(2, 416)}$ = 22.176, $p<0.000001$, Effect size: 0.2167, Power: 0.9507, post hoc, acquisition vs. generalization p = 0.00002, retrieval vs. generalization p = 0.00002.)

Discussion

The Rutgers Acquired Equivalence Test [4] was originally developed in order to learn about the visually guided associative learning of neurological patients with basal ganglia and

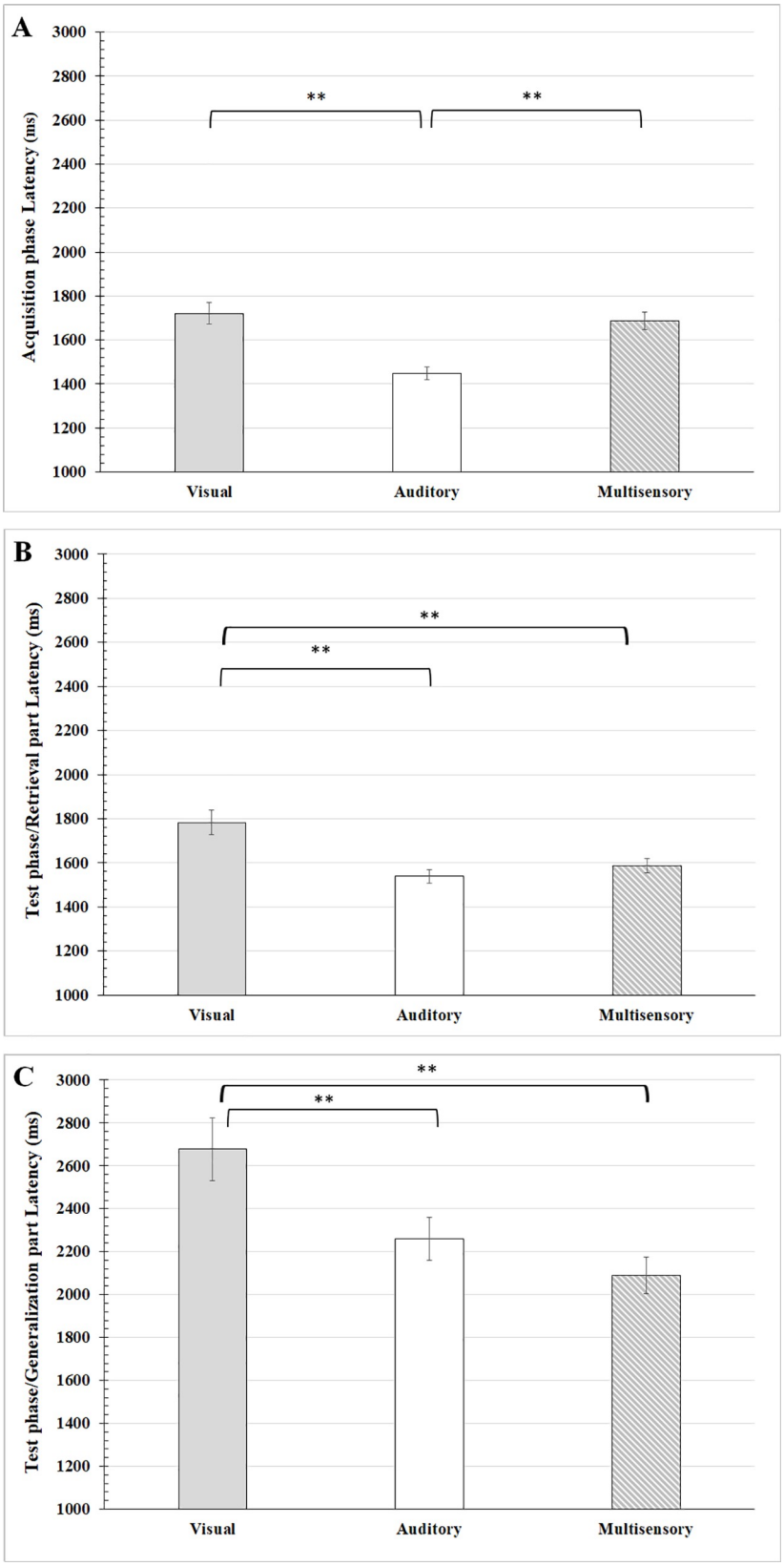
A
Acquisition phase Latency (ms)
3000
2800
2600
2400
2200
2000
1800
1600
1400
1200
1000
**
**
Visual
Auditory
Multisensory
B
Test phase/Retrieval part Latency (ms)
3000
2800
2600
2400
2200
2000
1800
1600
1400
1200
1000
**
**
Visual
Auditory
Multisensory
C
Test phase/Generalization part Latency (ms)
3000
2800
2600
2400
2200
2000
1800
1600
1400
1200
1000
**
**
Visual
Auditory
Multisensory

Fig 3. Response latencies in the sensory guided equivalence learning paradigms. (A) shows the response latencies in the acquisition phase of the paradigm, while (B) and (C) denote the response latencies in the retrieval and the generalization parts of the test phase, respectively. The ordinates show the latencies in millisecond (ms). Other conventions are the same as in Fig 2.

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hippocampus dysfunction. The test was applied later in cases of psychiatric disorders [41] and also to healthy subjects [6, 42]. Although both the basal ganglia and the hippocampi process not only visual but also multisensory information [10–13] the multisensory guided acquired equivalence learning had not been investigated before. As we recognized this absence we developed a multisensory (audiovisual) version of the associative learning test and were the first to investigate the basal ganglia and hippocampus mediated multisensory guided associative learning in healthy humans. We have to mention here that the aim of the study was not to measure directly the contribution of the involved structures to the paradigms. Thus, we could draw only indirect conclusions about the contribution of the basal ganglia and the hippocampi to the learning paradigms based on our psychophysical results and the results of previous publications in this field [4, 5, 7, 8]. This is a clear psychophysical study, which investigates the performance and the RT of healthy volunteers in different sensory guided associative learning paradigms.

The applied test can be divided into two parts irrespective of its modality. The first is the acquisition phase in which the subjects have to learn particular visual, auditory and multisensory stimulus combinations based on the feedback of the computer program. This process involves basal ganglia and the hippocampus. The association of new stimuli is dominated by the function of the basal ganglia [43, 44] and the coding and recall of associations are mainly a function of the medial temporal lobe [45]. Our results showed no significant difference between the performances (error ratio) in the unimodal visual, unimodal auditory and the combined audiovisual paradigms in the acquisition phase. Thus the modality of the stimuli does not affect the performance in this phase of the behavioral test. It is difficult to offer an explanation for this because it was described in several earlier studies that multisensory information could have more meaning than the sum of the unimodal ones [11, 46]. Multisensory integration has an important role not only in motor but also in cognitive functions of the brain. This multisensory facilitation plays a role in visual perception [47] object recognition [48, 49] emotional change recognition [50], face and voice recognition [51], or person recognition [52]. It affects the reaction time and accuracy of answers and the perceived threshold as well [27, 39, 53]. However, our results demonstrated absolutely no priority for the multisensory information in the acquisition phase of the applied associative learning paradigms. An explanation for this can be that such feedback based pair learning is a very old, conserved, and obligatory function which is so simple that the different modalities contribute to the association learning equally, and thus the multisensory information has no priority in these learning processes. This is in line with earlier findings that the basal ganglia, which are predominant in the acquisition phase of the associative learning test, are more active at the appearance of rare stimulus associations, which is not affected by modality [54]. It cannot be excluded that the semantic meaning of the stimuli could influence the performance in the learning paradigms. In a recent study it was demonstrated that semantically congruent audiovisual multisensory stimuli support multisensory integration [55]. In our experiment there was no attention paid to semantic contents because the task was the building of associations between the stimuli irrespectively of their meanings. As our stimuli were mainly semantically incongruent, this is another possible explanation for the lack of multisensory integration in the acquisition phase. At the behavioral level (opposed to the cellular level, [11] the presence of the multisensory integration is dependent on the level of attention and is not an automatic process [56].

The second part of the behavioral learning paradigm is the test phase, where the acquisitions learned earlier (retrieval) and hitherto not seen or heard pairs that were predictable by a previously deduced rule (generalization) were presented. The retrieval part of the test phase is dominated by the hippocampus-MT lobe system [45], and the generalization part of the test phase by the hippocampus and the basal ganglia [57]. Our results demonstrated that the performance was the most accurate (with the least incorrect answers) in the whole test phase of the multisensory guided paradigm although the multisensory performance differed significantly only from the auditory one, not the visual one. Thus, the multisensory-guided equivalence learning could be attributed mostly to visual learning, with the smaller benefit from the auditory modality. In the retrieval part, there was no difference between the unimodal tasks, but the performance in the multisensory task was significantly better than in the auditory one. Furthermore, in the generalization part, the performance in the unimodal visual task was significantly better than in the unimodal auditory one. Similarly, the performance in the multisensory task was significantly better than in the unimodal auditory one. We have to mention here the weakness of our study. The auditory guided task does not totally correspond to the visual and multisensory guided ones. Although all of the learning tasks contain eight stimuli, in the auditory paradigm the sound has to be associated not to a second sound but to a particular button on the keyboard, in contrast to the visual and multisensory tests where two visual stimuli or an auditory and a visual stimulus had to be associated. In an earlier draft of the auditory paradigm, we tried to apply one sound to each ear, but the participants would quickly become nervous and were not able to learn the acquisitions at all. However, the influence of this difference on the results cannot be explained by the auditory association to a keyboard button, as this seems to be an easier task than the visual and audiovisual associations. Nevertheless, the performances were worst in the auditory test.

The auditory and multisensory response latencies were not different but they were significantly shorter than the visual ones in the retrieval and generalization parts of the test phase. The most significant difference among the response latencies was in the generalization part of the test phase. If we compare the different phases of the paradigm, we can conclude that the generalization part of the test phase required the longest reaction times irrespective of the stimulus modality. This long decision time also supports that this is the hardest part of the applied cognitive learning task. We could not conclude that multisensory processing influences decision times, as would be suggested by Miller's race model [39], which reported that a multisensory stimulus can elicit a faster response even without integration actually occurring. In contrast to this finding, in the acquisition and the retrieval part of the test phase the multisensory response did not have the shortest latency. On the other hand, in the generalization part of the test phase, the multisensory response latencies were the shortest. However, based on the visual, auditory and audiovisual response latencies the Miller's race model was not violated [40]. This suggests that the shortest audiovisual response latency can be most probably explained by the race between the visual and auditory modalities and not by the multisensory (audiovisual) integration.

In summary, we can conclude that visual, auditory and multisensory guided association learning are similarly effective in healthy humans, which suggests that the primarily basal ganglia mediated acquisition phase is modality independent. On the other hand, in the test phase of the learning paradigm, which is dominated by the hippocampi, where the earlier-learnt acquisitions and hitherto not seen or heard but predictable associations are presented, the multisensory (audiovisual) stimuli elicited the best performance in the applied cognitive learning task. The test phase, especially its generalization part, seems to be a more difficult cognitive task than the acquisition phase, as the multisensory information processing could significantly improve the performance of the participants.

Supporting information

S1 Fig. Performances in the sensory guided equivalence learning paradigms. (A) denotes the number of the necessary trials in the acquisition phase of the paradigm. (B) shows the error ratios in the acquisition phase of the paradigm. (C) and (D) denote the error ratios in the retrieval and generalization parts of the test phase, respectively. In each panel, the first column (light grey) shows the results in the visual paradigm, the second column (white) denotes the results in the auditory paradigm and the third column (grey-white striped) demonstrates the results in the multisensory (audiovisual) paradigm. Mean ± SEM values are presented in each column. The black stars denote the significant differences. The single star in part C represents a significant difference, where $p<0.05$; the two stars in part D represent strongly significant differences, where $p<0.001$.
(DOCX)

S2 Fig. Response latencies in the sensory guided equivalence learning paradigms. (A) shows the response latencies in the acquisition phase of the paradigm, while (B) and (C) denote the response latencies in the retrieval and the generalization parts of the test phase, respectively. The ordinates show the latencies in millisecond (ms). Other conventions are the same as in Suppl. 1.
(DOCX)

S3 Fig. Test of the race model inequality. The figure represents the probability of cumulative frequency of response latencies in all three modalities (visual, auditory and audiovisual; x, y and z, respectively) and the sum of the two single modalities (x+y) in the generalization part of the test phase. The ordinate shows the latencies in milliseconds (ms) x 10^4. Based on these results the race model inequality can be kept, which contradicts the effect of crossmodal multisensory integration on the audiovisual (multisensory) response latencies in the applied learning paradigm.
(DOCX)

S1 File. Minimal data set. Worksheet titled "Results" contains the number of trials in the acquisition phase (NAT) and the number of errors in different phases of the tasks. Worksheet titled "RTs" shows the reaction times of all and the correct answers in different phases of visual, auditory and audiovisual paradigms.
(XLSX)

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Co-author certification

I, myself as a corresponding author of the following publication(s) declare that the authors have no conflict of interest, and Dr Anett Rosu Ph.D. candidate had significant contribution to the jointly published research(es). The results discussed in his thesis were not used and not intended to be used in any other qualification process for obtaining a PhD degree.

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The publication(s) relevant to the applicant's thesis:

1. EÖRDEGH, GABRIELLA; ŐZE, ATTILA; BODOSI, BALÁZS; PUSZTA, ANDRÁS; PERTICH, ÁKOS; ROSU, ANETT et al. (2019) Multisensory guided associative learning in healthy humans. PLOS ONE 14 (3), e0213094.

2. ROSU, ANETT; TÓT, KÁLMÁN; GODÓ, GYÖRGY; KÉRI, SZABOLCS; NAGY, ATTILA; EÖRDEGH, GABRIELLA (2022) Visually guided equivalence learning in borderline personality disorder. HELIYON 8 (10), e10823.