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

PhD thesis

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2023

Introduction

Learning and memory

Learning and memory are two basic functions of the nervous system that are essential to the full functioning and independent survival of humans and animals.

Learning refers to a change in behaviour that is the result of knowledge acquisition. It can be divided into subcategories based on the input modality (e.g., somatosensory, auditory, visual, etc.). Memory is the sum of processes that contribute to the encoding, consolidation, and retrieval of knowledge. Learning is the process, which makes the forming of memories possible, so it is analogous to the encoding process.

The classification of memory

In the model proposed by Atkinson and Shriffin in 1968, memory can be divided into three different, yet connected systems: the sensory register, the short-term store, and the long-term store. The sensory register stores the sensory information incoming from various sources and inputs only for a brief time (generally considered to be in the range of 1 second), after which the information decays. Short-term memory (also known as working memory) is the system interposed between the long-term store and the sensory register, so it receives input from both, and its functions are holding and manipulating information. The information held here also decays completely, though it takes a longer time (the timeframe is around 30 seconds). This modular model had been challenged and been replaced by a more complex one. A new element, a so called central executive system was introduced, which is connected to passive storages (where information is registered until fading or getting displaced) and active storages (which allow the manipulation of information, like updating or refreshing). The elements of this system are scattered across the neocortex, however the prefrontal

cortex, namely the ventrolateral and dorsolateral prefrontal cortices have a distinguished role in it.

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

Explicit memory

Explicit (also known as declarative) memory is a system that allows the conscious recollection of previously stored information. It can be further divided into two subdivisions: episodic and semantic memory, which are subsystems for personal experiences (i.e., memories concerning our lives, so called autobiographical memory,) and for facts (i.e., general knowledge about the world, like words and concepts), respectively. Explicit memory is roughly homogenous in both structure and function. It is centred around the medial temporal lobe (MTL) its key structures being the hippocampal formation and adjacent cortices.

Implicit memory

Implicit (also known as nondeclarative) memory is expressed through performance rather than conscious recollection, as the bits and pieces of knowledge acquired through this system are skills and procedures (such as riding a bicycle). Because of this, the implicit system has been proposed as a kind of fine tuning of the perceptual-motor system through experience. It is anatomically diffuse and covers a diverse functional range

Equivalence learning in general

Acquired equivalence (AE) is a learning paradigm, which tests both explicit and implicit learning functions, as it is based on the formation of relationships between previously unrelated items. During this type of learning, generalization is induced between two superficially different stimuli (the so-called antecedents) that have been associated with similar outcomes (the consequents) previously. Less vaguely it means that participants learn that two (or more) stimuli are mapped onto the same responses or outcomes, thus they are equivalent in this respect.

Regions of the brain involved in the AE

Medial Temporal Lobe

A pivotal part of the long-term memory is the medial temporal lobe (MTL) which consists of the hippocampal and the anatomically related cortical areas: the parahippocampal, perirhinal and entorhinal cortices. The hippocampal formation is well known as an essential structure of encoding and retrieval of explicit information and of spatial memory. This structure processes information from all sensory modalities, visual information included hence it has been considered to play a key part in visual learning.

Other structures associated with the declarative memory are the medial thalamus, the inferior temporal cortex and the prefrontal cortex.

Basal Ganglia

The basal ganglia form a network of interconnected subcortical nuclei that include the caudate nucleus and the putamen, the external and internal parts of the globus pallidus (GPe and GPi), the pars reticulata (SNr) and pars compacta (SNc) of the substantia nigra (SN) and the subthalamic nucleus (STN). The basal ganglia exert their main functions primarily through cortico–basal ganglia–thalamo–cortical loops, however loops that originate subcortically have been identified as well. These nuclei, in turn project either directly to the thalamus, midbrain and medulla, or indirectly through the thalamus to cortical and

limbic regions from which the original input to the whole network emerged.

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

Obsessive compulsive disorder and learning

Obsessive compulsive disorder (OCD) is affecting around 2-3% of both adult and child-adolescent populations, thus being one of the more prevalent human psychiatric disorders. It is possible for several different types of obsessions to form as a result of OCD, with compulsions emerging to counteract or mitigate these obsessions. Unfortunately, the exact pathogenesis of OCD is not fully understood yet, however we have knowledge of several alterations involved in OCD. Compared to healthy controls, different neurobiological abnormalities can be found, resulting in both morphological and functional changes. Structural and functional imaging of OCD patients has revealed higher cortical activation in the limbic and frontal associative cortices and the connected deep brain structures in the basal ganglia and hippocampi. Hence it seems that the cortico-basal ganglia-

cortical loops are strongly involved in the pathogenesis of OCD. Concerning memory and learning functions, the results of these studies are far from being uniform. Both verbal and nonverbal memory functions had alterations in some of them but were not affected according to others. However, to our knowledge, there was no information about the non-verbal learning of acquisition acquiring and the connected memory processes in pediatric OCD patients. Acquired equivalence learning is connected to the above-mentioned frontal cortex-basal ganglia loops and hippocampi but has not yet been investigated in children or adolescents with OCD. Since OCD is primarily connected to the dysfunction of the cortical-basal ganglia loops, our hypothesis was that the acquisition phase of the acquired equivalence learning test could be affected.

Tourette syndrome and learning

Tourette syndrome (TS) is a disorder presenting before the age of 18 years and affects 1% of school-aged children. The exact pathogenesis of TS is still unclear, however several underlying alterations are already known. The most frequent symptoms are motor and vocal tics, which significantly improve in many patients by young adulthood. In addition to the primary symptoms, pure Tourette syndrome is also associated with mild alterations in cognitive functions, mainly involving executive functions (such as verbal fluency, working memory and Stroop effect), which can extend into adulthood and others, which disappear with age (e.g. deficits demonstrated by the Wisconsin Card Scoring Test). The symptoms of TS are mostly related to dysfunction of the basal ganglia and the connected frontal lobe areas. Beside the functional alterations, reduced left caudate nucleus volume, prefrontal hypertrophy and other structural changes were also described in TS. The connection between the frontal cortex and the basal ganglia via frontostriatal circuits is significantly weaker in TS. This frontostriatal system is responsible for motor- and several cognitive functions. Descriptions of significant impairment in cognitive functions are rare in patients with pure TS and the impairment often depends on the level of tic severity. Most deficits

were reported in TS with its most frequent comorbidity, attention deficit hyperactivity disorder (ADHD). Previous information shows that most alterations of cognitive functions are mainly present with concomitant TS and ADHD. These results suggest that the cognitive performance of patients with TS and ADHD is more similar to that of patients with ADHD than that of patients with TS only. However, hippocampus-related learning was not affected in patients with TS alone. Interestingly, implicit probabilistic sequence learning, which is another type of procedural learning was not affected or was even better in patients with TS. The mentioned learning functions are mediated via frontostriatal loops, as well as associative learning, which, to our current knowledge, has not yet been investigated for TS.

Aims of the study

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

Specific objectives of our studies were:

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

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

Materials and methods

Participants

There were three different groups of children participating in the investigations with a visually guided associative learning task: patients diagnosed with TS, OCD and healthy controls. All participating children and their parents were informed about the background and goals of the study as well as the procedures involved. It was also emphasized that the participants were free to quit the study at any time (no one did so), and no compensation or benefit was given at the end of the tasks. Each participant and parent signed an informed consent form. The protocol of the study conformed to the tenets of the declaration of Helsinki in all respects, and it was approved by the Ministry of Human Capacities, Budapest, Hungary (11818-6/2017/EÜIG). The control groups were selected and matched from our larger database of children, recruited from local schools (Szeged, Csongrád-Csanád county, Hungary), free from any known psychiatric, neurological, neurodevelopmental, otologic or ophthalmic condition. All children in the patient groups and the control group were white.

OCD group

The conducted study included 31 pediatric OCD patients without any comorbidity (n_{male} = 18), aged 7.5–17.5 (mean, 12.63 ± 2.72). All participants were free of ophthalmological, otological, neurological, or psychiatric conditions besides OCD. Of the 31 children diagnosed with OCD, 16 were being treated with medications at the time of the tests (medicated group), while the other 15 were medication free during and before the investigation (unmedicated group).

From our database of healthy children, 31 control children (n_{male} = 18; mean age, 12.63 ± 2.73 years; range, 7.5–17.5 years) were assorted, who were matched one-to-one to the patient group by age, sex and intelligence level.

TS group

Altogether, 46 children with Tourette syndrome (TS) participated in the study (n_{male} = 32, mean age: 11.64 ± 2.38 years, age range: 8–17 years). A total of 21 patients were diagnosed with Tourette syndrome without any other neurological or psychiatric comorbidities (TS group); 15 were diagnosed with Tourette syndrome and comorbid ADHD (TS + ADHD group); and 10 were diagnosed with Tourette syndrome and some other comorbidity (obsessive compulsive disorder [OCD] or autism spectrum disorder [ASD]; TS + OCD/ASD group). Twelve of the children involved in this study (3 from the TS group, 6 from the TS + ADHD group, and 3 from the TS + OCD/ASD group) were medicated because of the symptoms of their disorder(s).

From our database of control children, 46 children (n_{male} = 31, mean age: 11.55 ± 2.38 years, range: 8–17.5 years) were assorted and individually matched to the patient groups by age, sex and intelligence level.

Visually guided associative learning paradigm

Myers and colleagues have developed a learning paradigm to investigate a specific type of associative learning, visually guided equivalence learning, that is called Rutgers Acquired Equivalence Test (RAET). In this test the participants have to acquire associations between antecedent stimuli (faces of cartoon characters) and

consequent responses (drawings of fish of different colour) through trial and error. The test is divided into three different parts: acquisition (learning of face-fish pairs based on feedback), retrieval (recalling the previously learnt associations) and generalization (application of associations in previously unseen but deducible pairs), the last of which needs further elaboration. Unbeknownst to the participants, the associations follow a regularity. During the second part of the test, they have to apply this regularity for pairs that were not presented in the acquisition part (thus transferring or generalizing the regularity).

Data analysis

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

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

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

Results

OCD patients

Because colour blindness two children were excluded from the data analysis, so the data of 29 pediatric OCD patients with their matched healthy controls is presented.

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

Our results revealed no significant differences between the performances of the two investigated groups (OCD vs. control). The median of the NAT in the OCD group was 59.0 (range: 44–290, n = 29) and 67.0 (range: 42–139, n = 29) in the control group (Mann-Whitney rank test U = 402, p = 0.779). The median of the ALER was 0.0612 (range: 0.00–0.4103, n = 29) for the OCD group and 0.0725 (range: 0.00–0.2446, n = 29) for the control group (Mann-Whitney rank test U = 426, p = 0.938). The median of the RER was 0.0556 (range: 0.00–0.1667, n = 29) for the OCD group and 0.0556 (range: 0.00–0.25, n = 29) for the control group (Mann-Whitney rank test U = 404, p = 0.8). The median of the GER was 0.0833 (range: 0.00–0.6667, n = 29) for the OCD group and 0.0833 (range: 0.00–1.00, n = 29) for the control group (Mann-Whitney rank test U = 371, p = 0.431). The RTs were also compared and no significant differences were found.

The effect of medication on the performances of patients with Obsessive Compulsive Disorder

Since we intended to investigate whether medication could have an effect on the performances, the performances of the two patient (medicated and unmedicated) and their matched healthy control subgroups were compared in a quadruple multiple comparison with

Kruskal-Wallis ANOVA test. The results revealed no significant differences ($p > 0.05$) among the four subgroups in any of the investigated metrics (NAT, ALER, RER, and GER).

TS patients

The performances of the entire Tourette syndrome group with and without comorbidities versus healthy control children

The median NAT was 79.0 (range: 42-202, n = 46) in all patients with TS (with and without medication) and 62.0 (range: 46-124, n =46) in the control group. The NAT values were significantly higher in patients with TS (Mann–Whitney rank test $U = 636$, $p < 0.001$). The median ALER was 0.102 (range: 0–0.325, n = 46) in all patients with TS and 0.085 (range: 0–0.186, n = 46) in the control group. The ALER values, similar to the NAT values, were significantly higher in patients with TS (Mann–Whitney rank test $U = 690$, $p = 0.004$). In the retrieval part of the test phase, there was no statistically significant difference (Mann–Whitney rank test $U = 1.17e+0.3$, $p = 0.360$) between the patients with TS (median: 0.056, range: 0–0.333, n = 46) and the control group (median: 0.083, range: 0–0.472, n = 46). In the generalization part of the test phase, similar to the retrieval part, there was no statistically significant difference (Mann–Whitney rank test $U=1.26e+0.3$, $p = 0.103$) between the patients with TS (median: 0.125, range: 0–0.667, n = 46) and the control group (median: 0.167, range: 0–0.917, n = 46, Fig. 2).

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

Unmedicated pediatric patients with Tourette syndrome versus healthy control children

In all unmedicated patients The NAT (Mann–Whitney rank test, $U=345$, $p = 0.004$) and ALER (Mann–Whitney rank test $U = 392$, $p = 0.023$) values were significantly higher in patients with TS. In the retrieval and generalization parts of the test phase there was no

statistically significant difference between the TS and the control groups.

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

Comparing the performances of the whole patient group (TS, TS + ADHD, and TS + OCD/ASD) with the unmedicated patient group (TS, TS + ADHD, and TS + OCD/ASD), no significant differences were found in any of the recorded parameters.

Medicated versus unmedicated pediatric patients with Tourette syndrome

The performance of the medicated patient group did not differ significantly from the performance of the unmedicated patient group in any of the recorded parameters.

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

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

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

Discussion

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

The remaining visually guided equivalence learning is an interesting finding because the majority of earlier studies showed that cognitive functions were altered in OCD patients (i.e., implicit sequence learning spatial attention and nonverbal memory and only in rare cases did not find significant impairments in cognitive functions). Because of the strong involvement of the frontal cortex-basal ganglia loops in the pathogenesis of OCD, the hypothesis of the present study was that the first part of the paradigm, the acquisition phase, which mainly depends on the function of the basal ganglia, would primarily be affected. However, the OCD patients could build the associations with the same effectiveness as the matched healthy control children. There are two possible explanations for this unaffected learning function. First, an explanation could be the compensatory function of the hippocampi of the basal ganglia dysfunction. This is in line with previous findings in which the hippocampi were able to compensate for the basal ganglia dysfunction in neurodevelopmental disorders. The second explanation is that OCD primarily affects the ventral (limbic) but does not affect or has a much weaker impact on dorsal frontostriatal loops.

Similarly, to the remaining acquisition function, the retrieval and generalization parts of the test phase, which primarily depend upon the function of the hippocampus-MTL—a system that is less involved in the pathogenesis of OCD than the BG-frontal cortex loops—were not altered either.

The question is raised as to whether the same performances in the psychophysical results were not due to the longer response times of the OCD patients. One argument could be that the longer response times of the OCD patients resulting from their compulsions could enhance their performances and decrease the number of bad decisions. However, similarly to the performances in the psychophysical tests, there were no differences between the response times of the OCD patients and the

healthy control children. Thus, the participants with OCD took no more time to make decisions than the healthy controls.

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

The alteration of visual associative learning in children with TS is an interesting finding because only in rare cases have significant impairments in any cognitive functions been described in TS. TS is strongly related to the dysfunction of the BG and the frontal associative cortex. Given the involvement of the BG in the pathogenesis of TS, the acquisition phase, which mainly depends on the basal ganglia, was primarily affected in the associative learning test. Based on our results, all patients with TS made the associations with less effectiveness than healthy control children. However, the retrieval and generalization parts of the test phase, which mainly depend on the function of the hippocampi, were not negatively affected by TS. Although the acquisition building was weaker, better performances (not statistically significant however) were found in the latter two parts of the paradigm, probably as a compensation of the hippocampus-MTL. Our results demonstrated that in the acquisition phase, the performance (NAT and ALER) of all patients (TS, TS + ADHD, and TS + OCD/ASD) was significantly weaker than in matched healthy control group. The question arises whether the alterations in equivalence learning in all patients with TS were primarily due to TS or its most common comorbidity, ADHD. In most cases, TS and ADHD, which seems to play a major role, are jointly responsible for the alterations in cognitive functions. The performance of the three different patient groups were compared and no significant difference were found among them. This finding does not support the predominant role of ADHD in the described alterations in the acquisition phase of the associative learning task. The comparison of each patient group with its matched healthy control group revealed significantly increased NAT or ALER values in patients with TS without any comorbidities and TS + OCD/ASD but not in patients with TS + ADHD. These results together could suggest

that concomitant ADHD and TS was not primarily responsible for the visual acquisition learning deficits in patients with TS. This is in contrast with previous findings that ADHD is primarily responsible for the alteration of cognitive functions in patients with TS + ADHD. Therefore, the visually guided acquired equivalence learning, similar to stimulus-response or habit learning which is mediated by the dorsal frontostriatal pathways, is more attributable to TS than ADHD, despite ADHD symptoms affecting the dorsolateral frontostriatal circuits. The volume of the hippocampi is significantly larger in patients with pure TS than that of their healthy counterparts, and no explicit memory (which is connected to the hippocampus) deficits were reported in children with TS. Our results are in line with these findings. The performance in the retrieval and generalization parts of the test phase, which are primarily related to the hippocampi was not worse in the entire group of patients with TS with and without comorbidities. Concerning the three investigated subpopulations of the patients with TS (TS without comorbidities, TS + ADHD, and TS + OCD/ASD), the RER and GER values did not differ from those of the matched healthy control children.

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

Conclusion

In the previously described two studies, we managed to examine the performance of children with OCD or TS and compare it to age, sex and IQ matched groups of children without any neurological and psychiatric condition.

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

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

Acknowledgements

First and foremost, I would like to thank my supervisor, Dr. Attila Nagy, who were my guide in scientific research from the students' scientific circle through the thesis and this PhD work. He also was my

very first boss and a role model in many aspects, let it be research, teaching or life outside of academia, for which I will always be grateful.
I would like to thank Professor Gábor Jancsó and Professor Ferenc Bari for letting me participate in the Neuroscience PhD program and I am also grateful to Professor Gyula Sáry for allowing me to do the necessary research in the Department of Physiology.
I would like to thank Dr. Gabriella Eördegh for her help with scientific writing, engaging conversations on our long trips and for always having my back.
A thank you goes out to Dr. Balázs Bodosi, who developed the software background and helped with anything informatics related.
I am grateful for my collegagues in the laboratory, namely Dr. András Puszta, Dr. Balázs Barkóczi, Diána Nyujtó, Xénia Katona and Viktória Balikó, for creating a place where it was always pleasurable to work. A special thank you is for my fellow PhD student, Zsófia Giricz, without whom I could not have crossed the maze of academy bureaucratics and deadlines. I am grateful to my colleagues in the Department of Physiology, namely Dr. Zoltán Lelkes and Dr. Ferenc Domoki, for helping me become a better educator and being an unending source of Physiology knowledge.
I would like to thank all the students who I had the opportunity to teach in the past years. It was a wonderful experience and you truly helped me become a better teacher and a better doctor, while fueling my passion for education.
I would like to express my gratitude to my family, my mother, Hedvig Mercz, my father, Antal Pertich and my sister, Flóra Pertich, who helped me on every step of my journey, believed in me and put up with me during the harder parts.
And finally, I would like to thank everyone who inspired or helped me: friends, family, colleagues, and teachers.

List of publications related to the subject of the thesis

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