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NEUROPSYCHOLOGICAL CHARACTERISTICS OF TREATMENT RESISTANT OBSESSIVE-COMPULSIVE PATIENTS; TENDENCIES IN DECISION MAKING PROCESSES

Theses of a Doctoral Dissertation

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THEORETICAL INTRODUCTION

The term obsessive-compulsive disorder (OCD) denotes a syndrome consisting of obsessions and compulsions, and OCD is currently listed among anxiety disorders (DSM-IV-TR) based on the DSM-IV-TR diagnostic manual.
OCD is a little known field in the psychiatric/psychological professional community, there are only a few research groups dealing with it worldwide contrary to depression and schizophrenia, which are better researched.
In the past 30 years considerable headway has been made in terms of research into OCD, unfoldment and reclassification of its symptoms; identification of its neuroanatomical structures and assessment of its neuropsychological features. However, research groups do not agree on what neuropsychological features characterise the disorder, and as for the cognitive profile of OCD data are contradictory even in scientific literature; or it is a question how neuropsychological deficits can correspond to the neuroanatomical structures identified in the disorder and what therapeutic relevance these correspondences may have. One of the main reasons for contradictions is that our way of thinking about diseases has considerably changed in the past few years.
Neuropsychological research today is not aimed to determine the cognitive profile or deficit that characterise a given disease, but to identify a cognitive marker (through research into markers a potential endophenotype might be revealed) or a functional disorder that describe a characteristic method of functioning (e.g. set-shifting deficit, decision making deficit) and they try to identify this method of functioning in different diseases (e.g. OCD, schizophrenia). So today's research has the goal of identifying a cognitive marker, even in different diseases, and possibly assigning this marker to certain areas in the brain.
Out of all brain regions the role of the prefrontal cortex has long seemed to be important in psychiatric diseases, functional disorders of the prefrontal cortex play a part in most psychiatric diseases (Fuster, 1997, Roberts, 1998). We can get information about the functioning of the prefrontal cortex in the following ways:

1. Structural neuroimaging studies: CT, MRI
2. Functional neuroimaging studies: fMRI, SPECT, PET
3. EEG, event related potential studies
4. Cognitive tests

In the present dissertation I am going to discuss information obtained through cognitive tests.

The prefrontal cortex is of vital importance when it comes to cognitive functions, it is a well-known fact that damage to the prefrontal cortex entails disorders in higher cognitive functions. Symptoms linked with damage to the prefrontal cortex are collectively referred to as dysexecutive syndrome, whose symptoms include damage to processes that require higher integrative functions such as decision making, planning, or central executive functions. The phenomenon was originally described during examining frontal lobe damaged patients, analysis of frontal lobe damage started in the 19th century with the famous case of Phineas Gage (Damasio, 1996). Later on most observation was focused on changes brought about by frontal leukotomy carried out in the 1940s and 1950s; Lurija described the symptoms of dysexecutive syndrome that accompany injury to the prefrontal cortex: behavioural rigidity, fluctuation, perseveration, decision making deficit, flexible planning and execution disorders (Lurija, 1973). Specification of certain areas and different functions of the prefrontal cortex was started in the 80s, in the famous E.V.R. case they managed to differentiate the special decision making deficit assignable to the ventromedial area of the prefrontal cortex (Saver,

1991). These observation and research trends have directed attention to functional disorders of the frontal-prefrontal cortex in connection with several psychiatric diseases, such as schizophrenia, depression and also OCD.

Three areas of the prefrontal cortex (the orbitofrontal cortex - OFC; the dorsolateral prefrontal cortex – DLPFC and the anterior cingulate cortex – ACC) are involved in several psychiatric diseases to different extent and with different emphases. From the perspective of obsessive-compulsive disorder the workings of the three areas of the prefrontal cortex and those of basalis ganglions (nucleus caudatus, globus pallidus, putamen, nucleus subthalamicus, substantia nigra) are of outstanding significance. The main regions of the prefrontal cortex and the functions assignable to them are the following:

1. OFC: originally, ideas about the orbitofrontal cortex looked at this area as a kind of an integrating centre (Krawczyk, 2002). Theories like these assume that OFC is active in situations when the individual has to make fast behavioural changes in order to be able to adjust to changes in the environment. OFC also plays a vital role in the process of social learning: it is a central region for the individual to define and highlight significant signs and also to compare them to previous experiences (Rolls, 2000). These ideas can be further specified today: OFC is important when it comes to learning rewarding, executing emotions and social behaviour, it integrates these functions when social skills are developed. Lesion studies indicate differentiation (and connection) between OFC and vmPFC (Huey, 2008). Operations of OFC are important in learning situations when the different responses have different outcomes (Schoenbaum, 2006). OFC is important in the estimate and expectation of future outcomes, so it works in situations that we can call ambiguous (uncertain uncertainty) as opposed to risks (certain uncertainty) (Schoenbaum, 2010). The orbitofrontal cortex is active in reward dependant decision making situations and when achieving motivating goals; it directs decision making processes that involve both reward and punishment, it becomes active in case of decisions that involve multiple options, and also positive and negative aspects. Its injury entails impulsivity, in which making high-risk decisions plays a part. In OCD, hyperfunctioning of the orbitofrontal cortex can be identified, so neuroimaging methods justify the fact that in case of OCD OFC is hyperactive, the patient's behavioural responses to environmental impulses are unjustifiably intense, which show themselves as uncontrolled thoughts and actions (Friedlander, 2006). Hyperfunctioning of OFC raises the question of the disorder's connection with addictions.

2. DLPFC: the dorsolateral prefrontal cortex is the other centre of higher cognitive functions. Maintaining goals, analysing possibilities and future outcomes; the ability to compare and estimate, constantly monitoring the hierarchy of competing possibilities and goals, and high functions of planning are in connection with this region (van den Heuvel, 2005). DLPFC plays a role in recognising new rules during executive functions as well as in keeping them up mentally and updating them. In case of injury to the DLPFC, goal oriented behaviour planning is damaged (Baxter, 1998). DLPFC is responsible for a reduced level of behavioural repertoire, for repetitive behaviour (Langen, 2011). In major depression this brain region's defective functioning can be related to reduced attention functions, and to the disorder concerning retaining new knowledge. In OCD DLPFC hypofunction may be assumed (Cummings, 1993) and this points towards the relatedness of OCD and mood disorders.

3. ACC: anterior cingulate cortex: it is responsible for analysing conflict processes and outcomes, and forecasting error probability (Bar-On, 2003, Krawczyk 2002). Increased activity of ACC is responsible for the feeling "something is not right" as well as for the

emotional assessment of the consequences of one's actions (Aouizerate, 2004). Functional neuroimaging methods have proved that ACC is a vital participant in several cognitive processes, such as attention, motivation, reward and error detection, working memory, problem solving situations (Bush, 2000). Hyperactivity in this area has been observed in numerous psychiatric diseases (phobias, OCD, depression) (Baxter, 1999), increased cingulate activity (inner feeling of insecurity, error detection) indicates that OCD is related to anxiety disorders. In OCD disfunctioning of ACC is related to several cognitive deviations (see inhibition functions, error detection), but psychosurgery methods have also made it probable that the anterior cingulate cortex plays a part in the pathophysiology of the disorder (the target area of anterior cingulotomy is this region).

In contemporary research the main questions concerning cognitive tests that map the functioning of the prefrontal lobe are as follows:
1. What are the main domains of our cognitive operations?
2. Which prefrontal areas are active during accomplishing a given cognitive task?
3. In psychiatric diseases where a prefrontal disorder has been justified by neuroimaging, and tests also justify a cognitive disorder, how can a given damaged cognitive function be linked to the operations of a given brain area?

In the present dissertation I will investigate two issues: on the one hand I am going to focus on a special group of OCD patients, treatment resistant patients, on the other hand I am going to investigate a cognitive function, the issue of decision making.

As for OCD, investigating treatment resistant patients is a field little researched into, though almost 40% of patients are affected by it (Lopez, 2004). We consider OCD patients treatment resistant when they do not give appropriate therapeutic reaction to an adequately applied combination of pharmaco- and psychotherapy either. Adequate pharmacotherapy treatment means applying SSRI medication (at least three types of medication at maximum dose level for 12 weeks) and standard augmentation strategies (two atypical antipsychotic medications). Adequate psychotherapeutic treatment means applying behaviour therapy (minimum 30 hours) (Husted, 2004).
Treatment resistant patients' condition shows a continuously declining tendency, besides decay in their mental condition, and somatic and psychosocial functions they more often also commit suicide (Rasmussen, 1997, Mindus, 1995).
Among treatment options for treatment resistant patients psychosurgery methods have also appeared in the past decades. Psychosurgery methods cannot be understood without the so-called loop theories that play a decisive role in OCD.
Loop theories express concentric relations and interactions between neuroanatomical structures affected by the disease. Modell described the pathological working model of the orbitofronto-striato-pallido-thalamic loop (Modell, 1998). In this model the hyperactivity of OFC and the nucleus caudatus path is responsible for the excessive drive; while decline in the inhibiting effects that basal ganglia exert on the thalamus is in correlation with the decline in inhibition functions that can be measured with neuropsychological tests and also dominate the clinical picture. Saxena modified Modell's theory and described the model of direct and indirect fronto-striato-pallido-thalamic loops (Saxena, 1998). The direct loop has a stimulating, while the indirect loop has an inhibiting effect on the thalamus; in OCD the workings of the direct and indirect loops are out of balance. Obsessive-compulsive symptoms can be decreased if the (inhibiting) effect of basal ganglia increases or orbitofronto-striatal activity decreases. Pharmacotherapy (SSRI medication), psychotherapies and psychosurgery also strive to achieve the latter result.

Currently, instead of circles operating in a parallel way theories of interconnections presume that these circles are much better integrated through the striatum and the thalamus than it was previously thought (Yin-Knowlton, 2006, Milad, 2012).
Among psychosurgery methods irreversible and reversible forms are distinguished; in OCD out of the irreversible methods cingulotomy, subcaudate tractotomy, limbic leukotomy and anterior capsulotomy are the procedures applied; while out of the reversible methods deep brain stimulation (DBS).
Losing balance in the fronto-striato-pallido-thalamic-fronto circle at some point in this complicated system may throw the state of self-regulation off balance, so it is based on this phenomenon that a certain consequently overactive area can be switched off or inhibited with psychosurgery methods, and by this means balance can be restored (Valálik, 2010). At the same time psychosurgery methods give the possibility of observing the workings of neuropsychological functions that can probably be assigned to path systems in cases when there are interventions in the path systems. (Csigó, 2008).
In the present dissertation I will focus on anterior capsulotomy from among irreversible procedures, and out of reversible ones on deep brain stimulation of the anterior branch of the capsula interna.
In international literature we have knowledge of only a few studies that have investigated the neuropsychological functions of patients treated with such psychosurgery methods. They describe considerable contradictions in terms of how interventions in path systems influence neuropsychological functions.
Studies dealing with anterior capsulotomy can be divided into two groups, in one of them there is a clinical survey before and after the operation, and they strive to justify the effectiveness of the operation (Oliver, 2003, Christiansen, 2002, Mindus, 1994). In the other group of studies though – and it is mainly characteristic of research groups working in big examination centres – it is part of the pre- and postoperative examination to take neuropsychological tests, too, by which they measure not only the effectiveness of the operation, but they also focus on changes in the cognitive profile characteristic of OCD (Fodstadt, 1988, Nyman, 1995, Mindus, 1995, Rück, 2003). Results from studies supplemented with neuropsychological tests can hardly be compared because of the low number of elements and the use of test batteries differing from one another, these studies contain contradictory results.
As for deep brain stimulation of the capsula interna data are only available from case studies for the time being. Case studies describe several contradictions in terms of neuropsychological tests. A certain number of studies prove the fact that there is no measurable cognitive change as a result of DBS (Abelson, 2005, Huff, 2009, Wayne, 2009); while other studies report about improvement of certain indicators: memory (Gabriels, 2003, Aouizerate, 2004), set-shifting (WCST) (Aouizerate, 2004). Case studies also inform about negative results: increased perseveration (Gabriels, 2003).

The other topic of the present dissertation is the issue of decision making.
Analysing scientific literature OCD shows a high level of heterogenity not only in clinical symptoms, but also in terms of cognitive deficits. Most research groups agree that the neuropsychological profile of OCD is dominated by damage to the executive functions.
The executive functions in the model – of Miyake et al, (2000) – can be divided into 3 main components – updating, set-shifting, inhibition; in the neuropsychological model of OCD it is relevant to analyse these 3 components. At the same time these 3 main executive components are in close interaction with each other in case of numerous tasks; all three components play a

part in decision making processes. It is an underlying question to clarify the relationship between executive functions and the ability to make decisions.
The decision making process means handling complex information, during which several components of executive functions will come into action: choosing possible options, choosing action; inhibiting alternative actions; experimental recording of output results (Paulus, 2007). As for the issue of decision making processes in case of OCD it is important to identify the healthy and defected workings of the following cognitive components: the ability of creating a strategy and set-shifting; being sensitive to feedback, sensitivity to reward and punishment. If we look at the studies that examine executive functions and decision making, we will find that executive functions do not show close correlation with the decision making performance (Toplak, 2010). In other words, decision making and executive functions can be considered as distinct constructs.
Scientific data in the literature about neuropsychological studies are contradictory when it comes to assessing if there a decision making deficit in the background of OCD. Starcke explicitly states that there is a decision making deficit behind OCD's clinical symptoms, he explains OCD's clinical symptoms with a decision making deficit (Starcke, 2010). But how can we grasp the phenomenon of decision making with tests? The most common assessment tools of decision making are the Iowa Gambling Test (IGT) and the Wisconsin Card Sorting Test (WCST). In the present dissertation I am going to investigate the question of decision making with the help of the Iowa Gambling Test and another little known card sorting test – the California Card Sorting Test – CCST, which has several advantages over WCST. CCST measures the problem solving component of the ability to make decisions. In the original version worked out by Delis in 1992 participants get 6 cards in 3 series, and in the first series (free vard sorting situation) they have to sort the cards into two groups from as many points of view as possible, and they have to label the viewpoints involved in sorting. This is the task of category forming. In the second situation participants have to recognise two sorts formed by the experimenter, and they have to label the viewpoint involved in sorting. The third series is the so-called directed situation when the experimenter tells the participant how to sort the cards. There has been experience about the test so far in case of patients suffering from depression (Fossatti, 2001), Parkinson disease (Dimitrov, 1999) and schizophrenia (Beatty, 1994). The test has not been used with OCD patients yet.
Applying IGT in case of OCD the data available in scientific literature are contradictory. In relation to IGT certain research groups have proved that OCD patients perform worse than normal controls (Cavedini, 2002), other research groups have proved that only certain subgroups of OCD do worse (Nielen, 2002, Lawrence, 2006). We also have knowledge of an assessment which did not find a difference between the performance of OCD patients and normal controls (Chamberlain, 2007).

OBJECTIVES

Present dissertation is aimed at mapping neuropsychological differences characteristic of OCD, with special regard to the treatment resistant subgroup, as well as dealing with practical applicability options of the results gained from theoretical and assessment data. The main objectives of my studies are as follows:
1. Identifying cognitive differences in treatment resistant OCD patients, studying how clinical symptoms and neurocognitive profiles of patients change during a rehabilitation treatment, or if they change at all.

2. How are treatment resistant OCD patients' clinical symptoms and cognitive profiles influenced by an irreversible psychosurgery intervention (anterior capsulotomy) during long term follow-up.
3. How are treatment resistant OCD patients' clinical symptoms and cognitive profiles influenced by a reversible psychosurgery intervention (deep brain stimulation) during follow-up.
4. How decision making processes shape up in case of OCD patients compared with normal controls.

LATEST SCIENTIFIC RESULTS

1. Thesis

Comparing two groups of treatment resistant patients treated with different methods (pharmaco- and psychotherapy/psychosurgery), both patient groups have shown significant improvement in their clinical symptoms during long term follow-up. The neuropsychological performance of patients treated with pharmaco- and psychotherapy did not show significant changes (1)

I followed up 10 treatment resistant OCD patients assessing both their clinical symptoms and neuropsychological functions. I defined criteria for treatment resistancy as it is described in the Theoretical Introduction. Out of the 10 patients 5 underwent anterior capsulotomy, and the other 5 had pharmaco- and psychotherapy treatment. I assessed patients treated with psychosurgery before the psychosurgery intervention, and 1, 6, 12 and 24 months after it. I assessed patients treated with pharmaco- and psychotherapy before treatment, and 1 and 6 months after that. I measured clinical symptoms on Y-BOCS, HAM-A and HAM-D scales, and from among neuropsychological tests I applied MAWI, the Verbal Fluency Test, the Category Fluency Test, Trail Making Tests A, B; the Pieron Test, the Corsi Test, the California Card Sorting Test, the Iowa Gambling Test and the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS). I matched the two groups of patients according to their cognitive profiles, how severe their clinical symptoms were at the beginning of the treatment, as well as according to their sex, age and level of education. According to my results both groups of patients showed significant improvement considering their clinical symptoms (Y-BOCS test), but patients treated with anterior capsulotomy showed a more marked improvement in their symptoms (20 points), while the Y-BOCS value of patients treated with pharmaco- and psychotherapy remained in the severe stratum in spite of a significant improvement in their symptoms. There was no measurable significant improvement in the neuropsychological performance of treatment resistant patients taking part in the pharmaco- and psychotherapy treatment program. At the same time, there was significant difference between the two groups of patients in 3 of the 10 neuropsychological tests: the partial trial of Trail Making Test B, the values of the RBANS Attention Index and the RBANS Language Index were significantly better at the 6 months follow-up of the patient group treated with pharmaco- and psychotherapy.

2. Thesis

During follow-up, patients treated with anterior capsulotomy showed significant improvement in certain neuropsychological tests: Verbal Fluency, Stroop Test, California Card Sorting Test. (1)

In Hungary there have been 5 patients undergoing anterior capsulotomy so far, and I followed up these patients for 2 years. I assessed patients treated with psychosurgery before the psychosurgery intervention, and 1, 6, 12 and 24 months after it. I measured clinical symptoms on the Y-BOCS scale, and from among neuropsychological tests I applied MAWI, the Verbal Fluency Test, the Category Fluency Test, Trail Making Tests A, B; the Pieron Test, the Corsi Test, the California Card Sorting Test, the Iowa Gambling Test and the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS). In terms of neuropsychological tests severe neuropsychological deficits were indentifiable in treatment resistant patients before anterior capsulotomy, all tests applied showed cognitive deficits, and a certain part of the deficits remained even during follow-up. Deficits were characteristic primarily in attention functions (Trail Making Test A, B), set-shifting functions (perserverative tendencies in Fluency Tests) and spatial working memory (Corsi Test). During follow-up there was significant improvement in IQ values (MAWI), patients found significantly more categories in the California Card Sorting Test, they generated significantly more words in the Verbal Fluency Test and they performed significantly faster in the interference trial of the Stroop Test. If we consider time changes as well, changes in the IQ value and improving performance in the Stroop Test appeared as early as in the first month after surgery, while improvement in the Verbal Fluency performance in the first year after surgery, while improvement in the California Card Sorting Test in the second year after surgery.

3. Thesis

Patients (OCD and OCD+Tourette) treated with deep brain stimulation showed improvement in their clinical symptoms during follow-up, and showed significant improvement in the task assessing inhibition functions (2)

In Hungary there have been 4 patients undergoing deep brain stimulation (with psychiatric diseases) so far (2 OCD patients, 1 OCD+Tourette patient and 1 patient diagnosable with Tourette syndrome). In the present dissertation I will impart assessment data concerning 2 OCD and 1 OCD+Tourette patients. I carried out clinical and neuropsychological assessments before deep brain stimulation and 3, 6 months and 3 years (with one OCD patient) and 2 years (with the OCVD+Tourette patient) after it. During follow-up all three patients showed improvement in their symptoms on the Y-BOCS and Y-GTSS clinical survey scales, the improvement did not reach a significant level at the 6 months assessment. From among the neuropsychological tests applied (the Verbal Fluency Test, the Category Fluency Test, the California Card Sorting Tests A, B; Trail Making Tests A, B; RBANS, the Iowa Gambling Test, the Stroop Test, the Corsi Test) task A of the Stroop Test showed significant improvement, which means improvement of reaction time and not the improvement of inhibition functions. Tendency-like improvement happened in the partial trial of RBANS measuring immediate memory. There was no difference in the rest of the neuropsychological tests (neither improvement nor decline). Analysing raw data of the three patients: the Trail Making Test and the RBANS Attention Index differentiate between patients; performance of

the OCD+Tourette diagnosed patient is intact, good, while in case of the 2 patients diagnosed with OCD the attention deficit remains even after stimulation.

4. Thesis

Decision making processes in OCD patients compared with normal controls show a deficit: patients' performance in the California Card Sorting Test and the Iowa Gambling Test is significantly worse.

In my investigations into decision making processes I compared 40 OCD patients with 40 normal controls, assessing decision making processes with the help of two tests – the Iowa Gambling Test (IGT) and the California Card Sorting Test (CCST). The two assessment groups were matched by sex, age and level of education. I used the manual versions of both tests. According to my results OCD patients found significantly fewer categories in the partial trial of CCST A; they identified significantly fewer categories in the partial trial of CCST B; they made more mistakes both in partial trial A and B than controls; and in the partial trial of CCST B there was a significantly higher number of persevered category identifications compared to the control group.

There was also a significant difference between the two groups in the IGT Test, OCD patients choose from a disadvantage pack of cards significantly more often, and they are less apt to choose the advantage pack of cards compared to controls. Healthy people's learning graphs shown during the IGT Test differ from those of OCD patients, OCD patients do not learn the advantageous strategy. Based on the results OCD patients are characterised by decision making deficits: the set-shifting function that is also part of the decision making process becomes injured; insensitivity to feedback is a characteristic feature; getting stuck with one strategy; insensitivity to consequences of decisions. The decision making strategy identifiable with OCD patients: sensitivity to immediate rewarding and insensitivity to punishment. These results refine the learning theory model of the disease: during the IGT Test it can be observed that the behaviour with immediate reward is imprinted, while patients are insensitive to punishment. Neuropsychological results can also be paralleled with clinical symptoms: compulsions in this sense can be considered as immediate rewards.

Making use of research results:

The present research, on the one hand contributes to a more precise identification of neuropsychological differences in OCD, and on the other hand it aims to clarify issues that scientific literature does not deal with (follow-up of treatment resistant patients) or does not give a clear picture of (decision making deficits). Results of my research that are targeted at identifying neuropsychological deficits can well be applied in clinical practice, results in connection with decision making have relevance in planning and modifying psychotherapy, primarily in cognitive behaviour therapy. The area of my dissertation that analyses special treatment possibilities for treatment resistant patients helps apply psychosurgery methods in a secure way, it contributes to refining professional guidelines of the method, as well as taking us closer to a better understanding of the pathomechanism of the disorder through the research.

Scientific publications related to the theses

(1) Csigó, K., Harsányi A., Demeter Gy., Rajkai Cs., Németh A., Racsmány M.: Long-term follow -up of patients with obsessive-compulsive disorder treated by anterior capsulotomy: A neuropsychological study *Journal of Affective Disorder* 2010. 126. 198-205.

(2) Csigó Katalin, Döme László, Harsányi András, Demeter Gyula, Racsmány Mihály: Deep brain stimulation for treatment refractory obsessive-compulsive disorder – a case report *Clinical Neuroscience/Ideggyógyászati Szemle* 2010, 63 (3-4): 137-142.

(3) Csigó Katalin, Harsányi András, Demeter Gyula, Németh Attila, Racsmány Mihály: Terápiarezisztens kényszerbetegek műtéti kezelése *Psychiatria Hungarica* 2008. 23(2): 94-108.

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