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EXECUTIVE FUNCTIONS, PROSPECTIVE MEMORY AND RETRIEVAL – CONTRIBUTION OF EXPERIMENTAL COGNITIVE PSYCHOLOGY TO THE UNDERSTANDING OF OBSESSIVE COMPULSIVE DISORDER

PhD thesis

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Budapest, 2012

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Acknowledgements

First of all I would like to thank my family for their ever lasting support in so many ways and for their love during these years. Without you all this work would never have been possible.

I am grateful to my supervisor, Dr. Mihály Racsmány who introduced me to the field of Cognitive Neuropsychiatry Research. He inspired me and constantly guided me to look behind the data and to try to comprehend the findings in a new theoretical frame.

I owe many thanks to the Nyírő Gyula Hospital Psychiatry Clinic 2 for helping me in organizing all the experimental work, especially to my research colleagues, Csigó Katalin and András Harsányi, MD, for their extraordinary effort in putting together the patient sample, for their valuable comments and professional support.

I am thankful to the patients who participated in the studies and who showed many human aspects of the "condition" not really described in the psychiatry textbooks thereby inspiring and teaching me.

I am especially thankful to my young research colleague Attila Keresztes for the discussions, his motivation and collaborative work.

I would like to also thank Professor Csaba Pléh who with his cognitive psychology classes in Kolozsvár raised my interest toward the domain of cognitive science and was a model and motivator also in the following years.

I owe thanks to the Márton Áron College and to the ProProgressio Foundation for the scholarships granted.

Glossary of abbreviations

ACC	Anterior cingulate cortex
anlOFC	Anterolateral orbitofrontal cortex
ANOVA	Analysis of variance
BVRT	Benton Visual Retention Test
CANTAB	Cambridge Neuropsychological Test Automated Battery
CANTAB SRM	Cambridge Neuropsychological Test Automated Battery - Spatial Recognition Memory Task
CANTAB SWM	Cambridge Neuropsychological Test Automated Battery - Spatial Working Memory
CBTT	Corsi Block Tapping Task
D	Depressive patient
dACC	Dorsal anterior cingulated cortex
DAT	Delayed Alternation Test
dCAU	Dorsal caudatus
dlPFC	Dorsolateral prefrontal cortex
DSB	Digit Span Backward
DSF	Digit Span Forward
DSM	Diagnostic and Statistical Manual of Mental Disorders
ERP	Event related potential
fMRI	Functional magnetic resonance imaging
HAM-D	Hamilton Depressive Rating Scale
HC	Healthy controls
ID/ED	Intradimensional/Extradiemsional Set-Shifting Task
lOFC	Lateral orbitofrontal cortex
MD	Multiple demand system
mOFC	Medial orbitofrontal cortex
n.s.	not significant
NAC	Nucleus accumbens
NRP	Unpracticed items from unpracticed categories
OAT	Object Alternation Test
OCD	Obsessive compulsive disorder
PAM	Preparatory attentional and memory processes model

PDA	Panic disorder with agoraphobia
PET	Positron emission tomography
PFC	Prefrontal cortex
PM	Prospective memory
PRMQ	Prospective Retrospective Memory Questionnaire
PUT	Putamen
rCBF	Regional cerebral blood flow
RCFT	Rey Complex Figure Test
RIF	Retrieval induced forgetting
RP-	Unpracticed items from practiced categories
RP+	Practiced items
RT	Reaction time
SAS	Supervisory attention system
SCH	Schizophrenic patient
SEC	Sroop Test - Errors color naming condition
SEI	Stroop Test - Errors interference condition
SEII	Stroop Test - Error inhibition index
SER	Stroop Test - Errors reading condition
SI	Stimulus independent
SO	Stimulus oriented
SP	Social phobia
SRI	Serotonin reuptake inhibitors
SRTC	Stroop Test - Reaction time color naming condition
SRTI	Stroop Test - Reaction time interference condition
SRTR	Stroop Test - Reaction time reading condition
STAI	Spielberger State and Trait Anxiety Inventory
STAI-S	Spielberger State Anxiety Score
STAI-T	Spielberger Trait Anxiety Score
vmPFC	Ventromedial prefrontal cortex
VOCI	Vancouver Obsessive Compulsive Inventory
WBSI	White Bear Suppression Inventory
WCST	Wisconsin Card Sorting Task
WCST-CL	Wisconsin Card Sorting Task - Conceptual level response
WCST-CN	Wisconsin Card Sorting Task - Number of categories completed

WCST-LS	Wisconsin Card Sorting Task - Failure to maintain set
WCST-NE	Wisconsin Card Sorting Task - Nonperseverative errors
WCST-NT	Wisconsin Card Sorting Task - Number of trials to complete first category
WCST-PE	Wisconsin Card Sorting Task - Perseverative errors
WCST-TA	Wisconsin Card Sorting Task - Trials completed
WCST-TE	Wisconsin Card Sorting Task - Total errors
Y-BOCS	Yale Brown Obsessive Compulsive Scale
Y-BOCS CRS	Yale Brown Obsessive Compulsive Scale, Compulsions Severity Score
Y-BOCS ORS	Yale Brown Obsessive Compulsive Scale, Obsessions-Severity Score
YBOC-SC	Yale Brown Obsessive Compulsive Scale Checklist

Abstract

The exact nature of the neurocognitive deficit behind the clinical symptoms in obsessive-compulsive disorder (OCD) is still unclear. There is a growing amount of evidence about the executive system deficit in OCD, which is strongly connected to the fronto-basal loop dysfunctions of the disorder. The theoretical background of our research on executive functions rests on the psychometric model proposed by Miyake et al., (2000). Through latent variable analyses, this model defines three main components of executive functions: updating/monitoring, shifting and inhibition. In our research we assessed the executive functions of OCD patients and healthy controls. This approach led to evidence about the impairment of the shifting and inhibition components and to the description of the relations between symptoms and different neuropsychological indices.

In our view the executive system deficit in OCD is strongly related to the specific prospective memory (PM) dysfunction. This ability makes possible to retain, to recall and to execute an intention in the appropriate time and context of the future. An important phase comes after the realization of the intended actions: the cancellation of the successful action representations after attaining a goal. This phase could be impaired in OCD. In this setting the goal can be achieved by the constant monitoring of the environment or by the periodical refreshing of the intents and strategic and automatic processes are also involved. According to our view in OCD we face a hyperactivity of the PM system resulting in constant monitoring of the environment. We hypothesize that the impaired inhibition component of the executive system is responsible for this hyperactivity. The patients commit significantly more errors and slow down in the event-based PM tasks' ongoing part than the matched control subjects. It is possible that OCD patients are unable to inactivate successfully realized intentions and due to inhibition deficit the previous task remains on their "to execute list". This contributes then to the observed obsessive-compulsive behavior. The missing of the retrieval induced forgetting (RIF) effect in OCD according to our results might be explained by the dysfunction of conflict detection processes. We have demonstrated this effect in a series of experiments with healthy adults. It persist also in the long term if there is no active rehearsal and a period of nocturnal sleep is included before the recall. We think that the inclusion and development of such tasks in the cognitive behavioral therapy of patients are essential to increase the effectiveness of inhibition mechanism and PM performance.

Kivonat

Az obszesszív-kompulzív zavarban (OCD) tapasztalt tünetek hátterében álló neurokognitív deficit természete még távolról sem tisztázott. Egyre több bizonyíték támasztja alá azt az elképzelést, hogy OCD-ben a végrehajtó rendszer károsodása érhető tetten, amely szorosan kapcsolódik a betegségben észlelt fronto-bazális körök deficitjéhez. A végrehajtó funkciókról való gondolkodásunk és az ezen a területen végzett vizsgálataink elméleti hátterét Miyake és munkatársainak (2000) pszichometriás modellje adja, mely latens változó elemzést alkalmazva a végrehajtó funkciókat három fő komponens – a frissítés, a váltás, és a gátlás - mentén rendezi. Kutatásunkban OCD betegek és egészséges kontroll személyek rövid távú emlékezeti és végrehajtó funkcióit vizsgáltuk standardizált neuropszichológiai eszközök segítségével. Eredményeink alátámasztják a váltási illetve a gátlási komponensek sérülését, rámutatva a tünetek és a neuropszichológiai mutatók közti összefüggésekre.

Elképzelésünk szerint ugyanakkor, kényszerbetegeknél a végrehajtórendszer deficittel szoros kapcsolatban, a prospektív emlékezet sajátos zavara figyelhető meg. Ez a képességünk teszi lehetővé, hogy egy szándékot megőrizzünk, felelevenítsünk és a jövő egy adott időpontjában, kontextusában kivitelezzünk. Szándékos cselekvések kivitelezését követően van egy lényeges mozzanat, éspedig a cél elérését követően a cselekvés leállítása, ami kényszerbetegségben sérült lehet. A cél a környezet folyamatos monitorozásával, vagy a szándék időnkénti frissítésével érhető el és ebben a folyamatban automatikus és akaratlagos mechanizmusok egyaránt részt vesznek. Elgondolásunk szerint OCD-ben a prospektív emlékezeti rendszer túlműködésével szembesülünk, ami a környezet fokozott monitorozásában nyilvánul meg. A túlműködés hátterében ugyanakkor a gátló végrehajtó mechanizmusok elégtelensége valószínűsíthető. A betegek szignifikánsan többet hibáznak, illetve szignifikánsan jobban lelassulnak az eseményalapú prospektív emlékezeti feladatokban, mint az életkorban, iskolai végzettségben illesztett egészséges kontrollok. Lehetséges, hogy nem tudják megfelelően inaktiválni a már sikeresen kivitelezett szándékaikat, így e gátlási mechanizmus kudarca miatt a korábbi feladat továbbra is a végrehajtandó program részét fogja képezni, hozzájárulva így az obszesszív-kompulzív viselkedéshez. Az előhívás kiváltotta gátlási hatás eltűnése OCD-ben eredményeink alapján a konfliktus detektáló folymatok diszfunkciójával magyarázható. E hatásról egészségeseken végzett kísérletsorozatunkban azt is kimutatjuk, hogy hosszú távon is fennmarad, ha nincs ismétlés és van egy közbeiktatott alvási periódus. Úgy gondoljuk, hogy a prospektív emlékezeti teljesítményt és a gátlási funkciók hatékonyságát elősegítő feladatoknak létjogosultsága van a betegek kognitív viselkedésterápiájában.

Introduction

In our daily life we repeatedly face situations when we check the locks of the door, or if turned off the stove or think about an upcoming stressful event. The problem is when these *obsessive* thoughts or *compulsive* rituals occur so regularly and so intensely that it interferes with the normal functioning of the individual.

From the perspective of a cognitive researcher there are a lot of open questions which need answers, just to mention a few: "What cognitive mechanism are involved in the persistence of obsessions and compulsions?"; "What executive functions are impaired in OCD and how do they relate to the main symptoms?"; "What is the role of inhibition in symptomatology?"; "Can different subgroups be described also by different neuropsychological patterns?"; "Is there a memory impairment in OCD?"; "What type of memory is impaired?"; "Is there a PM impairment?"; "How can we interpret the memory impairment patterns?"; "Is there a RIF effect and if not, why?"; "Which are the critical cortical structures and networks involved in OCD and how do they relate to the cognitive findings and symptoms?"; "What are the endophenotypic markers of OCD?"; "How can all these cognitive findings contribute to a better therapeutical outcome?".

The aim of this thesis is to give some insight to a few questions related to the cognitive function impairments in OCD.

The structure of the thesis is the following: In *Chapter 1* we present the main symptoms and clinical aspects of OCD. *Chapter 2* begins with a short review of the executive function concept, theories, and its assessment methodology. This chapter ends with a detailed presentation of main findings in OCD executive function research which are presented under three main domains: updating/monitoring, shifting and inhibition. *Chapter 3* is dedicated to the concept of PM, presenting the main theories in the field and focusing on the main findings in OCD. This chapter ends with a short outline of our theoretical point of view about the possible involvement of PM functions in OCD symptomatology and we summarize the role of inhibition in memory retrieval presenting the relevant connections with OCD. In *Chapter 4* we present three relevant neuropsychological models of the disorder and in *Chapter 5* we outline the most important questions and hypothesis of our research studies presenting the main goals and thesis points. Two published research articles, one accepted manuscript and two unpublished studies are included under the *Chapter 6*. Following the *Studies* is the *Discussion and Conclusion* Chapter where we try to integrate our findings with previously

reported work. The final Chapter, *Further directions,* we present a couple of relevant new directions in the cognitive function research of OCD.

Chapter 1. Overview of Obsessive compulsive disorder (OCD) - definition and main symptoms

Definition

Obsessive-compulsive disorder (OCD) is a highly debilitating neuropsychiatric condition characterized by intrusive unwanted thoughts (obsessions) and/or repetitive, compulsive behaviors, or mental rituals (compulsions) (American Psychiatric Association, 1994), and recent research produced compelling evidence for orbitofrontal and basal ganglia related neuropsychological dysfunctions (Brambilla, Barale, Caverzasi, & Soares, 2002; Busatto et al., 2000; Kringelback & Rolls, 2004; Lucey et al., 1997; Milad & Rauch, 2012; Saxena & Rauch, 2000;).

In the Diagnostic and Statistical Manual of Mental Disorders (DSM IV, 1994) OCD is grouped together with other anxiety disorders, outlining the central role of anxiety and discomfort, which are accentuated usually by the obsessions and ameliorated by compulsions (for the exact criteria see DSM IV, 1994).

Prevalence and comorbidity

The prevalence of the disorder is between 2-3% in the general population. International studies found mostly the same occurrence rate in different countries (Csigó, Harsányi, & Demeter, 2010; Montgomery & Zohar, 1999; Németh, 2000).

Based on epidemiological data in the general population the male/female ratio is 1:1. There are gender differences regarding the onset of the illness and main symptoms. More men are diagnostised with OCD in puberty and adolescence while in women the main onset is at the beginning of the 20s (Fontenelle & Hasler, 2008). Labad et al. (2007) found that more female patients were in the contamination obsession and cleaning compulsion dimension (Female/Male Odds ratio: 2,02) and less in the sexual and religious obsession dimension then male (Female/Male Odds ratio: 0,41).

OCD can occur concomitantly with other disorders: depression, anxiety, Tourette's disorder, panic disorder, phobias, tricotilomania, bulimia, anorexia (see Fineberg, Marazziti, & Stein, 2001; Rasmussen & Eisen, 1994).

Symptom dimensions – the question of heterogenity

Beside the unitary view of OCD outlined in DSM IV in the past decades it is conceptualized as a heterogeneous disorder and there were strong efforts to find and describe

different subtypes (for review see Harsányi, Csigó, Demeter, Németh, & Racsmány, 2007; McKay & Neziroglu, 2008; Sookman, Abramowitz, Calamari, Wilhelm, & McKay, 2005).

The symptom-based approaches were the most prominent ones and agree that the complains of OCD patients fall into one of several major categories: a) cleaning compulsions; b) checking rituals; c) obsessive thoughts alone; d) obsessional slowness; and e) mixed rituals (Jenike, Baer, & Minichiello,1998). Hodgson and Rachman (1977) in a seminal early work from this field found that 53% of their patients showed checking rituals, 48% cleaning rituals, 52% obsessional slowness and 60% doubting obsessions, demonstrating also that patients could have more than one type of major concern. Treuer, Németh, and Rózsa (2001) found the following pattern – symptom dimensions in a Hungarian population regarding frequency and coucurrence of major obsessions and compulsions:

1. obsessive fear of contamination (72%) with cleaning rituals (75%)
2. aggressive obsessive thoughts (63%) with checking rituals (72%)
3. obsessive thought related to sexual topic (27%) with repeating rituals (66%)
4. religious obsessive thoughts (43%) with praying rituals (15%)
5. obsessive thoughts related to ordering and symmetry (47%) with counting compulsions (35%).

Other researchers agreed in the following symptom dimensions: washing compulsions, checking compulsions and obsessions without compulsions (Burns, Keortge, Formea, & Sternberger, 1996; van Oppen, Hoekstra, & Emmelkamp, 1995). Baer (1994) conducted a principal component analysis of the YBOC-SC (Yale Brown Obsessive Compulsive Scale Checklist) and found three major factors: symmetry and hoarding; contamination and cleaning; and pure obsessions. Calamari et al. (2004) using cluster analysis found support for taxonomy with seven subgroups: contamination, harming, hoarding, obsession, symmetry, certainty and contamination/harming.

The second approach is represented by the neuroimaging studies, which try to found connections between the symptom dimensions and the functions, characteristics of specific brain areas. Rauch et al. (1998) found accentuated regional cerebral blood flow at the level of the striatum that was associated with checking rituals, while reduced activity was associated with dimension of symmetry and ordering symptoms. In case of washing and contamination dimension found increased activity bilaterally at the anterior cingular cortex respective at the left orbitofrontal cortex. Another researchgroup (Mataix-Cols, Wooderson, Lawrence, Brammer, & Speckens, 2004) in a functional MRI study focused on three main symptom dimensions and found that patients with cleaning symptoms showed increased activation

bilaterally at the ventromedial prefrontal cortex and at the right nucleus caudatus; patients with aggressive obsessive thoughts/checking compulsions at the putamen/globus palidus, thalamus and dorsal cortical areas while patients with hoarding symtoms at the left precentral gyrus and right orbitofrontal cortex. Gilbert et al. (2008) in a voxel based morphometrical study found connection between symptom dimensions, symptom severity and the reduced grey matter volume. In case of cleaning-washing dimension they described reduced grey matter at the level of Broadman 6 area in the right hemisphere, while found a tendency between reduced grey matter volume at the Broadman 6 area in the left hemisphere and hoarding dimension.

The third approach is represented by studies describing different neuropsychological profiles across symptom-based OCD subtypes. This research has focused mainly on patients with checking rituals (Sher, Frost, & Otto, 1983; Tallis, Pratt, & Jamani, 1999; Zitterl et al., 2001), although less common subtypes, such as hoarding (Wincze, 2001) and obsessional slowness (Hymas, Lees, Bolton, Epps, & Head, 1991) have also been examined. It has been found that checkers exhibit greater deficits in general memory, memory for actions, and decreased vividness of memory (Sher et al., 1983; Sher, Frost, Kushner, Crews, & Alexander, 1989; Constans, Foa, Franklin, & Mathews, 1995). In another study the authors have found (Lawrence, Wooderson, Mataix-Cols, David, & Specker, 2006) that patients' characterized with symmetry and ordering symptoms showed difficulties in shifting and the patients characterized dominantly with hoarding symptoms manifested difficulties in decision making. Hashimoto et al. (2011) in their study outlined that patients in the contamination/cleaning dimension performed better in the logical memory and shifting tests, while patients in the aggressive obsessive thoughts/checking compulsions dimension showed impaired performance on the shifting task and the patients from the symmetry dimension in the logical memory and shifting tasks.

All these results are compelling evidence supporting a heterogeneous approach of OCD and it begins to be clear that different cortical areas and pathways are involved in the appearances of specific symptom dimensions. Based on all these findings and on the a factorial analysis of Yale-Brown Obsessive Compulsive Scale (Y-BOCS) scores of huge number OCD patients (e.g., Leckman et al., 2007) most probably in the upcoming version of the DSM this heterogenic symptom based approach will be present containing 5 different subgroups:

1. aggressive obsessions with checking compulsions
2. sexual and religious obsessions

3. obsession related to symmetry and punctuality with repeating, ordering, counting rituals and compulsions
4. obsessions related to contaminations with cleaning compulsions
5. hoarding obsessions and compulsions

Chapter 2. The study of executive functions in OCD

2.1. The concept of executive functions

Executive function as so many cognitive psychological constructs is an *umbrella term* and a lot of researchers from the past decades understand very different processes and mechanisms by it.

The study of executive functions and the use of this terminology raise a lot of questions. This apparent contradiction may originate in the fact that the definition of the concept is not clear and is a theoretical one. Additionally, the executive system is not unitary and different researchers understand different cognitive mechanisms on it. For example Shallice and Evans (1978) refers to it as cognitive estimation, Shimamura, Janowsky and Squire (1990) as behavior initiation, Levine, Goldstein, Williams and Eisenberg (1991) as problem solving, Shallice and Burgess (1991) as planning and Baddely (1996) as attention control just to mention a few.

The studies in this field can be grouped in three main categories:

a) describing the connections between executive functions and the frontal lobe

b) focusing on the developmental aspects of executive functions in childhood, adulthood and normal ageing

c) focusing on the effects of different degenerative and psychiatric disorders on executive functions. According to Fodor (1983) executive processes are effortful, conscious and poorly understood compared to modular and automatic processes.

Baddely and Hitch (1974) respective Baddely (1996) have introduced the concept of central executive in the context of a working memory model, and thought that its main function is related to control and resource allocation. Many researchers and clinical practitioners prefer the use of executive functions instead of the concept of central executive, outlining their multidimensional aspect. According to Burgess (1997) we need executive functions:

- in planning and decision making situations
- in error detection and correction
- in new situations requiring a response which competes with habitual responses
- in situations when the links between the input schema control units are novel and not well learned
- in dangerous and difficult situations.

By the overview of literature we can also find other functions or abilities which were thought to fall under the term executive functions. To the Burgess (1997) list described above we can add the prioritizing and sequencing of behavior, set shifting, multitasking, behavior monitoring, inhibition of irrelevant information or stereotyped behavior, resistance to interference, utilizing relevant information, abstracting relevant, common elements, sustaining attention and the maintenance of intentions (Burgess, Veitch, de lacy Costello, & Shallice, 2000; Chan, Shum, Toulopoulou, & Chen, 2008; Damasio, 1995; Grafman & Litvan, 1999; Shallice, 1988; Stuss & Benson, 1986).

One important moment in the research of executive function was the recognition that the results from laboratory experiments are similar to the phenomenon observed in case of frontal lesions. Many theories have their origin in the neuropsychological study of frontal lobes.

The classical symptoms of *frontal syndrome* are the rigidity of the behavior, perseveration, planning and inhibition difficulties, inappropriate behavior in new situations, which were interpreted in the context of executive system impairment (Shallice & Burgess, 1991). The neuropsychological assessment of frontal syndrome faces difficulties due to the lack of valid and accurate executive tests and also because the syndrome itself is rather fractionated then unitary (Chan et al., 2008).

It can be said that the concept of executive functions is a theoretical and not an operational one, and doesn't have a proper screening, or a well defined set of neuropsychological tasks. For example if we want to study dysgrafia we have a set of tasks assessing different aspects of writing, and subjects who fail will be considered dysgraphics. But in case of executive functions we don't have a prototypical screening measure.

Since the connections between executive deficit and frontal impairment were well documented in clinical studies this issue was handled by selecting patients who had frontal lesions (Burgess, 1997). However, the picture is even more confusing if we take into consideration that the different methods used to evaluate executive functions require different cognitive processes.

From the overlooked definitions, approaches we can see that the common aspect is the idea that executive functions are thought of as a set of abilities required to guide our behavior toward a goal, especially in new situations and are essential critical in everyday life.

2.2. Theories and measurement of executive functions

There are many different approaches and theories regarding executive functions. In this chapter the focus will be only on those which are considered relevant from the aspect of test development and clinical application.

Luria's theory

Luria (1966, 1973) rejected the strict localizationist approaches regarding cognitive functions and cortical structures. In his functional theory he described three main units which are interconnected and the final behavior is determined by its dynamical interactions. The first is the *energizing unit*, responsible for regulating and maintaining arousal in the cortex and is linked to the brainstem. The second is the *information processing unit* responsible for encoding, processing, storing information and relies on the function of temporal, occipital and parietal lobes. The third is the *control unit* responsible for programming and regulating behavior and relies specially on the frontal lobe.

According to Luria damages to the prefrontal area of the frontal lobe will disrupt complex behavior planning and control. The tasks developed by Luria, - as the Simple finger opposition, the Fist-Fest-Palm Test, the Reciprocal Motor Programme Test - in today clinical setting are used as screening tests assessing motor initiation, sequencing and inhibition (Chan et al., 2008).

Baddely working memory model

In their seminal paper Baddely and Hitch (1974) have argued that short term memory is not unitary and introduced the model and concept of working memory, which they thought responsible for the short term maintenance and dynamical manipulation of different pieces of information (in Hungarian see Demeter & Racsmány, 2008).

The original working memory model had three main components: the *visuo-spatial sketchpad* responsible for short term storing and processing of visual and spatial information; the *articulatory loop* responsible for storing and processing of verbal information and the *central executive* which guides the function of the two subsystems and is responsible for the allocation and control of cognitive recourses. This simple model was one of the most fruitful theoretical concepts in the field of cognitive psychology inspiring immense set of research. Baddely (1986, 1990) compared the central executive to the supervisory attention system (SAS; Norman & Shallice, 1986).

The *dual-task paradigm* was developed and influenced by this framework which was often used in healthy subjects to study executive functions experimentally by accounting for the interference between concurrent tasks (e.g., Baddeley, 1986; Logie, Gilhooly, & Wynn, 1994). In this paradigm a target task is performed simultaneously with a secondary task thought to involve executive functions and if the two tasks interfere it is concluded that the target task also requires the executive component. One of the most frequent used secondary tasks in the context of working memory model was the *verbal random generation task* (Baddeley, 1986) in which subjects have to produce in stream letters or numbers as random in order as possible.

The dual task method has the advantage that it makes it possible to study the involvement of executive component in different target tasks, the use of different secondary tasks to tap different aspects of executive functions and offers the possibility to dissociate the executive processes from nonexecutive ones by the use of a huge range of verbal and visuospatial secondary tasks (Philips, 1997).

Supervisory Attention System model (SAS)

Luria conception about the prefrontal cortex, namely, the responsibility for programming, monitoring and controlling behavior had influenced the computational SAS model, characterizing the prefrontal cortex as SAS. The model states that actions are controlled on two levels (Burgess & Shallice, 1997; Norman & Shallice, 1986).

The first level, *contention scheduling*, is automatic and controls routine behaviors when environmental cues are sufficient to trigger appropriate behavior. However, contention scheduling is not always enough to secure an appropriate or intended outcome. At the second level SAS biases contention scheduling and monitors the environment for target cues that indicate when it is appropriate to execute the intended behavior. If the routine selection of actions is insufficient at the first level, for example in new situations, then the involvement of the SAS is necessary to help the cognitive system to achieve the most proper solution. This higher level control mechanism plays an important role in decision making, in error detection, in new situations requiring flexible outcomes as well.

The SAS model was extended also to multitasking performance in everyday life (Burgess, Veitch, de lacy Costello, & Shallice, 2000) and according to the authors multitasking behavior include eight different proper characteristics (e.g., engagement in only one task at a particular time period by the subject; unforeseen interruptions and unexpected

outcomes etc.) which in many laboratory based tasks are not taken fully into consideration. Evidence supporting this theoretical concept first of all comes from studies of patients with frontal lobe lesions (Chan, Hoosain, Lee, Fan, & Fong, 2003; Shallice, 1988) and from multitasking literature, when healthy subjects intentionally switch attention between different tasks face a considerable cost expressed in reaction time (Allport, Styles, & Hsieh, 1994; Burgess, 2000a, 2000b; Gilbert & Shallice, 2002; Rogers & Monsell, 1995).

The most relevant tools to measure executive functions developed based on the concept of SAS are: the Six Elements Test (Shallice & Burgess, 1991), Hayling Sentence Completion Test (Burgess & Shallice, 1996a) and Brixton-Spatial Anticipation Test (Burgess & Shallice, 1996b), Sustained Attention to Response Task (Robertson, Manly, Andrade, Baddeley, & Yiend, 1997), the Behavioral Assessment of Dysexecutive Syndrome (BADS) and Dysexecutive Questionnaires (DEX) (Wilson, Alderman, Burgess, Emslie, & Evans, 1996). To these we can add also those tests which were developed to assess executive attention and depend on the SAS. These include: a) tasks that involve conflict and interference as various versions of the Stroop test; b) tasks that involve shifting between different subtasks or categories as the Wisconsin Card Sorting Test (WCST), the Trail Making B test and verbal fluency tests.

Goldman-Rakic's working memory model

One main difference between the models discussed so far and this approach is that it is based on animal, especially on monkey studies. Working memory refers to transient representations of task relevant information and is critical for animals that are not stimulus driven in their behavior. Goldman-Rakic (1992) called working memory the "blackboard of the mind" and linked it to the lateral prefrontal cortex. In her model beside the role of the prefrontal cortex she emphasizes the importance of different catecholamines, especially dopamine in the modulation of inhibitory and excitatory commands between the prefrontal cortex and posterior brain areas.

The classical demonstration of these model assumptions comes from prefrontal lesion monkey's poor performance on the *delayed-response task*, which requires from the animal to sustain the representation of the previously seen food location during a delayed period. By the increase of the level of dopamine performance on this task is improving.

The model does not have its own set of battery or tasks but we can say that this concept of working memory together with Baddeley's (1986) approach had also influenced the

elaboration of a series of tasks in use in today`s clinical and experimental setting. Probably the most well-known ones are the Letter-Number Span Test (Gold, Carpenter, Randolph, Goldberg, & Weinberger, 1997) and the N-back Test (Callicott et al., 1998). These tests beside the simple storage of incoming information require also a dynamic maintenance and manipulation of representations, which tapes the executive component of working memory.

Duncan's goal neglect theory

In his theory Duncan (Duncan, 1986, 1995; Duncan &Owen, 2000; Duncan et al., 2000) argues that our behavior is guided by a set of goals and subgoals organized in a hierarchical pattern. The human behavior is goal oriented and our goals help us accommodate to the external and internal demands controlling the behavior by activation or by inhibition. Faced with a new task at the first stage of executive processing we analyze it and determine the goals and subgoals, weighting them and establishing a hierarchical plan of action which then will be carried out. Performance then will be monitored and evaluated in order to allow modifications if necessary. Patients with frontal lobe damage often fail to realize intended goals, which Duncan called "goal-neglect": the subjects are able to describe the tasks requirements, but during completion ignore them.

The authors had proposed that fluid intelligence as characterized by Spearman's g factor (1927) depends on the frontal lobe functions Patients with frontal lesions who achieved higher scores on the Wechsler Intelligence Test scored significantly lower on the fluid intelligence test, focused on problem solving (Duncan, Burgess, & Emslie, 1995).

Functional neuroimaging studies (Ducan & Owen, 2000; Duncan, 2006) discovered a common brain activity pattern, called the multiple demand system (MD) during very different cognitive tasks. This specific activity pattern involves the posterior part of the inferior frontal sulcus, the anterior insula and adjacent frontal operculum, the pre-supplementary motor area, the adjacent dorsal anterior cingulated and the intraparietal sulcus (Duncan, 2010). A similar activity pattern can be seen during problem solving tasks taping fluid intelligence (Duncan et al., 2000; Prabhakaran et al., 1997).

The MD cortex plays a crucial role in defining and controlling parts of mental programs which helps us to achieve different set of goals. According to Duncan (2010) while we are learning new tasks, the processes of fragmenting and assembling different parts of it enables strong MD activity.

As far as we know no executive task was developed from this theory. Robertson elaborated the Goal Management Training package, which became very useful in different therapeutical settings helping patients to be more effective in encoding goals and monitoring performance. Incorporates six stages: 1. *Stop* (let the patients ask and reflect on what they are actually doing); 2. *Define* (determining the main task, establishing priorities); *List* (listing the phases to complete the task); *Do it* (caring out the task); *Check* (monitoring the ongoing task).

Critical remarks and conclusion

As we can see from this overview there are different approaches and there is no gold standard task in the assessment of executive functions (for review see Rabbit, 1997). Very often, even the process required by certain tests or tasks is unclear. Frontal involvement was also demonstrated by modern neuroimaging studies in many cases (e.g., Carpenter, Just & Reichle, 2000; Stuss & Levine, 2002), but we know also that different cortical areas are also involved in the realization of these complex tests (e.g., Alvarez & Emory, 2006; Nyhus & Barceló, 2009)

According to Philips (1997), an executive task must involve a combination of novelty, effort and working memory. If we want to asses an individual planning strategy or goal attainment behavior we must use a novel task, otherwise we will test the subject already well practiced, previously formed strategies. Because one test can be novel just once, the test-retest reliability of this task is relatively low. The task must also be complex in the sense that involves hierarchically structured different goals which require an effort for planning, response inhibition and monitoring. In executive tasks the coordination and online processing of different pieces of information requires the involvement of working memory.

Another critical remark concerns the ecological validity of these tasks, because even though many patients can show relatively intact performance on these tasks, they cannot function properly in real life situations (Shallice & Burgess, 1991). There is a gap between neuropsychological test scores and everyday life functioning (Chan et al., 2008).

Today's clinical practice and experimental research face the need for understanding of deficits underlying different executive components and recent studies point toward a non unitary executive system and toward the development of new neuropsychological executive tasks, trying to integrate the information from cognitive, social and neuroscience.

2.3. Impairment of executive functions in OCD

According to recent findings, the primary cognitive deficit contributing to the OCD profile is dysfunction of the executive system (Olley, Malhi, & Sachdev, 2007). However, many studies have found less impaired or intact performance in traditional executive neuropsychological tasks for OCD patients (for reviews see Chamberlain, Blackwell, Fineberg, Robbins, & Sahakian, 2005; in Hungarian Demeter, Csigó, Harsányi, Németh, & Racsmány, 2008; Demeter, 2010a; Greisberg & McKay, 2003; Kuelz, Hohagen, & Voderholzer, 2004).

In this overview the most relevant research findings from this field are presented using the Miyake et al. (2000) psychometric model about executive functions. According to this approach, traditional neuropsychological executive tasks depend on three main central executive components: *modality-specific updating/monitoring*, *shifting* and *inhibition*. The authors used confirmatory factor analyses and structural equation modeling to find evidence supporting the unity and diversity of executive functions, and for this have preselected well known simple executive tasks (e.g., plus-minus task, stop-signal task, number-letter task etc.) which were considered to tape the above mentioned 3 main components of the executive system, as well as complex executive tasks as the WCST, the Tower of Hanoi, the random number generation and the dual tasking. The three latent variables were correlated but separable and contributed in different proportions to the performance on complex executive tasks. By structural equation modeling they find evidence supporting that WCST was related especially to shifting, the Tower of Hanoi to inhibition and the random number generation to updating executive functions.

In the overview below we will focus on these 3 main components and we will not discuss the results from other main executive domains as planning, problem solving and decision making.

Updating and monitoring

This component refers to refreshing the content of the working memory. Maintenance of task-relevant information is accomplished by monitoring and coding relevant incoming information, and replacing old information that is no longer task-relevant (Morris & Jones, 1990). The importance of updating is that it actively manipulates relevant information in the working memory, rather than passively storing information (Miyake et al., 2000).

The tasks that are most commonly used to test this function in the OCD literature are the *Letter Fluency Task* (e.g., Martinot et al., 1990), the *Letter Memory Task* (e.g., Morris and Jones, 1990), and the *N-back Task* (e.g., van der Wee et al., 2003). OCD patients usually perform poorly in the latter two tasks while the results regarding verbal fluency are more contradictory.

The test which has been used the most often to study lexical fluency in OCD is the *Controlled Oral Word Association Test* (COWAT) which requires from the subjects to generate in one minute as many words as they can with the given starting letter (e.g., F, A, S) following certain simple rules (e.g., cannot use proper names, inflections, repetitions). Just a few studies report reduced lexical fluency (Christensen, Kim, Dysken, & Hoover, 1992; Schmidtke, Schorb, Winkelmann, Hohagen, 1998) most studies find this capacity intact in OCD (Basso, Bornstein, Carona, & Morton, 2001; Jurado, Junqué, Vallejo, & Salgado, 2001; Martinot et al., 1990; Pujol et al., 1999; Roh et al., 2005; Spitznagel & Suhr, 2002; Zielisnki, Taylor, & Juzwin, 1991).

It is important to note that the time span used in different letter fluency task was some time different, making comparison of the results difficult. For example Zielinski et al. (1991) used a 5 minute period, while in the Sieg et al. (1999) study only one minute was given for each letter.

In contrast, some studies find low performance in semantic verbal fluency tasks, where subjects have to generate words from a predefined category in on minute (e.g., animals, fruits, vegetables) (Lacerda et al., 2003; Roh et al., 2005). This result may reflect reduced access to the semantic system in OCD (Olley et al., 2007).

While there is an impressive amount of data (for review see Kuelz et al, 2004) about impaired visual ability and visuospatial organization in OCD there are just a couple of non-verbal fluency studies using very different tasks and scoring techniques. Some report deficit (Mataix-Cols, Barrios, Sánchez-Turet, Vallejo, & Junque, 1999; Schmidtke et al., 1998), the others stand by intact functioning in OCD (e.g., Christensen et al., 1992).

From all these studies we can conclude that OCD patients have difficulties in semantic fluency tasks probably due to an accessibility problem but they perform in the normal healthy range regarding letter and design fluency. In future studies in this domain near the inclusion of a perfectly matched healthy control group (education, IQ, gender, handedness, no previous psychiatric diagnoses) a clinical control group will be very useful to help clarifying the specificity of the neuropsychological dysfunction in OCD.

Shifting

The shifting component of the executive system is responsible for coordinating the change between relevant and irrelevant sets. The task that is most often used to study the set-shifting abilities of OCD patients is the *Wisconsin Card Sorting Task* (WCST, Berg, 1948; Heaton, 1981). WCST is a complex task and depending on the structural equation modeling analyses used it mainly reflects the shifting component of the executive system (Miyake et al., 2000).

In the standard computer version of the task, four stimulus cards with symbols differing in colour, shape, and number appear on the top of the screen and the subjects had to match a target card which appeared on the middle of the screen with one of the four stimulus cards. After each placement, the subject is informed via a message on the screen whether the response is correct or incorrect. Participants are instructed to sort the target cards into piles under the reference cards according to one sorting principle. The subject has to get as many cards right as possible. After 10 consecutive correct matches with the first criterion (colour) the sorting principle is changed without warning to a second one (form), then to a third one (number) and the subject has to find the correct sorting strategy using the received feed-backs on the screen. The subject must be able to reject the old rule and to switch to the discovered new one. The procedure is repeated twice or until all of the 128 matching cards were used. The indices considered for the test evaluation are as follows: Trails administered, Total correct, Perseverative responses, Perseverative errors, Nonperseverative errors, Conceptual level responses, Categories completed, Trails to complete first category, Failure to maintain set and Learning to learn.

Some studies have described set-shifting deficits in OCD using the WCST (Boone, Ananth, & Philipott, 1991; Hymas et al., 1991; Mukhopadhyay et al., 2010; Okasha et al., 2000; Roh et al., 2005), but others have not (Abbruzzese, Ferri, & Scarone, 1995a, 1995b, 1997; Moritz, Fricke, Wagner, & Hand, 2001; Zielinski et al., 1991). Roh et al. (2005) in a more recent study have found that OCD patients commit more perseverative responses and errors on this task. Because this task was one of our main assessment tool for the shifting component of the executive system in our research (Study 1) we present at the end of this section a detailed overview of the studies using WCST from the literature (see Table 1 for details).

The results obtained on the *Object Alternation Task* (OAT, Freedman, 1990), Delayed Alternation Task (DAT, Freedman and Oscar-Berman, 1986) (Abbruzzese et al., 1995a; Abbruzzese et al., 1997; Gross-Isseroff et al., 1996; Moritz et al., 2001; Spitznagel and Suhr,

2002) and on the *Intra-Dimensional/Extra-Dimensional shifting task* (ID/ED) of the CANTAB battery (Purcell, Maruff, Kyrios, & Pantelis, 1998; Veale, Sahakian, Owen, & Marks, 1996; Watkins et al., 2005) seem to be more constant and point toward impairment in OCD.

In the OAT there are two different objects under which a target (e.g., money) can be hidden. The goal of the subject is to acquire as many targets as she/he can, by lifting only one object per each trail. On the first trail the objects contain the same targets, then either response will be considered correct. For the coming trails targets are hidden (the subject can not see the changes because of a paravan) under the object not previously chosen or if subjects select a wrong location the target remains under the same object. The location of the objects (left or right) is also varied pseudorandomly. Preservative errors are calculated by the number of incorrect choices of an object two or more times consecutively before strategy shift. The main difference in the DAT is that here the target is hidden under two identical objects (e.g., cups) and the side is the important variable (left or right).

OAT requires subjects to establish and maintain a cognitive set of alternation and subject must deduce the task rule through trial and error leanings. It is similar to the WCST in regards to giving feed-back for the subject after each trail, assisting participants to learn that the target alternates between two possible locations based on a simple rule.

The main difference could be that OAT does not require a shift toward another set and it measures a different aspect of preservative behavior from WCST (Freedman, 1990). According to another explanation (Chamberlain et al., 2005) the task measures behavioral reversal and in this interpretation frame, successful performance depends on the inhibition process, which is altered in OCD.

The contradictory results could be explained also by the different cortical areas involved in the realization of these tasks, suggesting the presence of a "double dissociation". While the WCST activates mainly the dorsolateral prefrontal cortex which is impaired dominantly in schizophrenia, the OAT the orbito- and ventral prefrontal areas, which are affected in OCD (Abbruzzese et al., 1995a; Abbruzzese, et al., 1997; Zald, Curtis, Folley, & Pardo, 2002). However, it is important to note that it is very difficult to ascribe set shifting dysfunction to a specific cortical area and it will be an over-simplification of the results, because the attention shift usually depends on the interaction of different brain areas. Current neuroimaging results also sustain a very diverse cortical network involvement in the realization of the WCST (e.g., Nyhus & Barceló, 2009).

The *ID/ED shift task* of the CANTAB battery is thought to be a "clear" set-shifting task and does not require from the participants to match-to-sample. This subtask is defined as a test of rule acquisition and reversal. It features: a) visual discrimination and attentional set formation, b) maintenance, shifting and flexibility of attention. Two dimensions are used in the test: colour-filled shapes and white lines. Feedback teaches the subject which stimulus is correct, and after six correct responses, the stimuli and/or rules are changed. These shifts are initially intra-dimensional (e.g., colour filled shapes remain the only relevant dimension), then later extra-dimensional (white lines become the only relevant dimension). If at any stage the subject fails to reach six consecutive correct responses after 50 trails, the test ends. This test has eighteen outcome measures, assessing errors, and numbers of trials and stages completed (CANTABeclipse, 2006).

A great advantage of this task compared to the WCST is that it allows the measurement of response latency. OCD patients performed worst in this task, needed more trails to reach criterion and more likely failed to complete all phases of the task than control subjects (Purcell et al., 1998; Veale et al., 1996; Watkins et al., 2005).

One important common result in all this reported shifting tasks is that OCD patients require more learning trails to reach a specified criterion, which could be interpreted also from the perspective of impairment at the level of feed-back use. This question needs further empirical research as the involvement of the orbitofrontal cortex in set shifting. So far we can say that OCD patients manifest impairments on those shifting task which are considered sensitive to orbitofrontal deficit.

Set shifting impairment in OCD is a highly debated topic in today's research literature and the missing of a straightforward result is probably due to a lot of factors. First, the different level of sensitivity of the tasks used to measure this ability have to be mentioned, second the unclear of the psychological functions involved in its realization, third the different and multiple brain areas involved and fourth the presence of confounding variables such as the severity of the OCD symptoms, the presence of different comorbid disorders, medication use and sample matching. An important step in this field will be besides the above mentioned the specification of the different roles played in the realization of the performance patterns by these confounding effects.

Inhibition

In the Miyake et al. (2000) model inhibition refers to one's ability to deliberately inhibit dominant, automatic, or prepotent responses when necessary. We discuss those paradigms and main results with OCD patients which can be integrated in this executive conceptual framework.

One of the most commonly used tasks to study inhibition processes in OCD patients is the *Stroop Task*, in which subjects have to inhibit a dominant response (i.e. reading the name of the colour as written) and produce an adequate response (i.e. naming the ink colour). The results of this task with OCD patients are contradictory. Martinot et al. (1990) found impairment in this task but other studies have reported a similar performance by the matched healthy control group (Aronowitz et al, 1994; Bannon, Gonsalvez, Croft, & Boyce, 2002; Boone et al., 1991). These differences could reflect the different methodology used and the heterogeneity of the OCD population.

Another paradigm used for the study of inhibition is the *Go/NoGo Task*, where the subjects have to give a motor response for a specific target (e.g., press a specific key on the keyboard) as fast as possible and to inhibit this response for the other very similar stimuli. Bannon et al. (2002) find that OCD patients commit significantly more false alarm type errors then patients with panic disorder. In another study where the performance of OCD patients was compared to healthy subjects there was no difference (Aycicegi, Dinn, Harris, & Erkmen, 2003) while other studies reinforced the lower performance of OCD patients (Penades, Catalan, Andres, Salamero, & Gasto, 2007; Watkins et al., 2005). Electrophysiological and neuroimaging studies had demonstrated low frontal activity during NoGo trails (Herrmann, Jacob, Unterecker, & Fallgatter, 2003) and the hyperactivity of the anterior cingular cortex during error commission on the NoGo trails (Maltby, Tollin, & Worhunsky, 2005).

In a very similar paradigm, the *Stop-Signal Task* subjects had to give a motor response by pressing a specific key if a green X appeared on the screen and inhibit this response if the colour of the X turned to read, OCD patients overperformed the healthy controls (Krikorian, Zimmerman, & Fleck, 2004). During this task researchers have found reduced activity at level of basal ganglions and right orbitofrontal cortex in OCD (Wooley et al., 2008).

Another paradigm frequently used for the study of flexible control mechanism and inhibition is the *Antisacade Task*. In this task the subjects are required to generate a saccade to the opposite site from the target presented in the peripheral visual field by inhibiting a reflexive urge to respond to that stimulus. Tien, Pearlson, Machlin, Bylsma and Hoehn-Saric (1992) find that OCD patients manifested a greater error and inaccurate saccade rate in a goal

guided antisaccade task. However, another study found no significant difference between the antisaccade error rates except on the latency of antisaccades which were slower in the OCD group (Maruff, Purcell, Tyler, Pantelis, & Currie, 1999). A more recent work also supports this finding, the OCD group showed higher frequencies of anticipatory saccades with reduced amplitudes only on the predictive saccade task (the timing, amplitude and direction of the targets are predictable) which relies mainly on the circuits between the frontal eye field and basal ganglia and presented a similar performance pattern as the normal subjects on the antisaccade task which predominantly involves the dorsolateral prefrontal cortex (Spengler et al., 2006).

From these findings it can be concluded that the results in these paradigms are strongly influenced by the characteristics of the tasks, by the exposition times, by the inter stimulus intervals, by the predictability of the targets and by the proportion of Go and NoGo responses which must be taken into account in futures studies. The low performance on cognitive and motor inhibition neuropsychological tasks supports the theory of frontostriatal dysfunction in OCD (Penades et al., 2007; Savage, 1998). Chamberlain et al. (2005) consider that deficits at the level of inhibition mechanism are responsible for the main symptoms and neuropsychological profiles in OCD.

As it can be seen through the overview of the most relevant findings from the executive functions literature the most common approach to investigate neuropsychological profiles in OCD has been to compare the performance levels on different neuropsychological tests to healthy controls.

There is a new direction toward the identification of different neuropsychological profiles for OCD subtypes and also toward the establishment of different subgroups based on the neuropsychological performance patterns (Nedeljkovic et al., 2009). Postulating that there is an executive function deficit in OCD is a very broad assumption, and our aim was to focus on the most relevant executive components: inhibition and shifting.

Table 1. Summary of OCD patients results in the WCST from previous research

Authors	Samples	Medication	Performance	Conclusions/Comments
Boone et al. (1991)	N=20 OCD N=16 HC	medication free for at least 4 weeks	impaired	right hemisphere and basal ganglia dysfunction
Hymas et al. (1991)	N=16 OCD patients with obsessional slowness N=15 HC	12 patients were medication free; 4 under medication	impaired	OCD patients with obsessional slowness might have dysfunctional frontal and basal ganglia system
Zielinski et al. (1991)	N=21 OCD N=21 HC	12 patients were medication free; 9 under medication	no difference	no impaired set shifting ability in OCD
Abbruzzese et al. (1995a)	N=35 OCD N=25 HC N=25 SCH	OCD patients treated with fluvoxamine	no difference	dysfunction of the orbitofrontal cortex in OCD and dysfunction of the dorsolateral prefrontal cortex in SCH
Abbruzzese et al. (1995b)	N=33 medicated OCD N=14 unmedicated OCD N=33 HC	OCD patients treated with fluvoxamine	no difference	OCD it is not associated with dysfunction of the dorsolateral prefrontal cortex
Gross-Isseroff et al. (1996)	N=15 OCD women N=15 HC women	medication free for at least 2 weeks	no difference	sample size; the question of gender
Abbruzzese et al. (1997)	N=60 OCD N=30 HC N=60 SCH	OCD patients treated with fluvoxamine; SCH patients with neuroleptica	no difference	dysfunction of the orbitofrontal cortex in OCD
Lucey et al. (1997)	N=19 OCD N=19 HC	12 patients were medication free for at least 3 months; 7 patients treated with fluoxetine or sertralin	impaired	involvement of the dorsolateral prefrontal cortex in OCD
Cavedini et al. (1988)	N=19 OCD N=19 HC	medication free for at least 1 month	no difference	selective impairment of orbitofrontal cortex in OCD

Authors	Samples	Medication	Performance	Conclusions/Comments
Zohar et al. (1999)	N=18 OCD females N=14 OCD male	medication free for at least 2 weeks	no difference	WCST performance negatively correlated with symptom severity in females and positively in males – sexual dimorphism in OCD
Deckerscbach et al. (2000)	N= 17 OCD	medication free for at least 2 weeks	no difference from statistical norms	no consistent association between shifting ability, verbal fluency, and memory scores
Okasha et al. (2000)	N= 30 OCD N= 30 HC	medication free for at least 2 weeks	impaired	frontocortical dysfunction in OCD
Basso et al. (2001)	N= 20 OCD N= 31 HC	3 patients were unmedicated	impaired	executive deficit is related to comorbid depression
Moritz et al. (2001)	N= 36 OCD N= 17 high depression score N= 19 low depression score N= 36 HC	20 patients were medicated	impaired – only patients with high depression score	the study of executive function in OCD must account for comormid depressive symptoms
Mataix-Cols et al. (2002)	N= 28 medicated OCD N= 24 unmedicated OCD	SRI-medicated vs. SRI-free fro at least 2 weeks	no difference	SRI don't have a significant impact on the WCST performance
Moritz et al. (2002)	N= 25 OCD N= 25 SCH N= 25 D N= 25 HC	14 OCD, 20 D and all SCH patients were medicated	no difference in OCD; just D and SCH group vs. control	need for more fine-grained tasks in the study of neuropsychological functions
Lacerda et al. (2003)	N=14 OCD N=14 HC	medication free	impaired	positive correlations were observed between nonperseverative errors and rCBF in frontal areas and anterior cingulated, while perseverative errors correlated negatively with rCBF in the right thalamus
Whitney et al. (2004)	N=11 OCD N=26 SCH with obsessive-compulsive symptoms N=28 SCH without obsessive-compulsive symptoms	all patients were under psychiatric treatment	no difference	comorbid individuals haven't demonstrated significantly lower performance, just a statistical trend could be observed

Authors	Samples	Medication	Performance	Conclusions/Comments
Roh et al. (2005)	N= 20 OCD N= 20 HC	undermedication	impaired	executive function impairment together with visuospatial memory and fluency deficit may underlay the pathology
Rao et al. (2008)	N=30 recovered OCD N=30 HC	28 patients were on SRI; 8 of them were also on clonazepam and one was on ziprasidone	impaired (completed category)	neuropsychological deficits are as candidate endophenotype markers for OCD; certain executive functions are probably state independent
Kitis et al. (2007)	N=23 OCD N=24 SCH N=22 HC	11 OCD patients were on antidepressant therapy, 2 were on combination of antidepressants and antipsychotics and 10 were medication free; from the SCH group 2 patients were medication free	no difference from HC; SCH performance was impaired compared to OCD	cognitive dysfunctions in OCD may be related to overvalued ideas; there were no significant differences in cognitive functions between SCH group and the OCD patients who had higher scores on the Overvalued Ideas Scale
Shin et al. (2008)	N=17 N=25ADHD N=21 tic disorder N=20 D N=23HC	six of the subjects in the OCD group were taking fluoxetine, sertraline or risperidone	impaired compared to HC	study with children; support near the fronto-striatal deficit hypothesis
Nakao et al. (2009)	N=40 OCD N=25 HC	medication free for at least 2 weeks	no difference (OCD patients tended to achieve fewer category)	symptom severity and symptom subtype such as obsessions/checking might affect neuropsychological dysfunction and related brain activities
Cavedini et al. (2010)	N=35 OCD N=35 unaffected first degree relatives N=31 HC	not mentioned	no difference	executive dysfunction as possible endopehontypic marker in OCD – decision making and planning
Mukhopadhyay et al. (2010)	N=20 OCD N=20 HC	not mentioned	impaired	it offers an approach to understand instinctual impulses from neuropsychological perspective

Authors	Samples	Medication	Performance	Conclusions/Comments
Bradbury et al. (2011)	N=10 High Beliefs OCD N=11 Low Beliefs OCD N=13 PDA N=13 SP	not mentioned	the High Beliefs OCD group performed significantly worst	argue near a possible connection between heightened obsessive beliefs and cognitive inflexibility
Krishna et al. (2011)	N= 31 medication-naive OCD N=31 HC	never treated	no difference	the importance of medication-naive studies

Note. OCD, obsessive compulsive disorder; SCH, schizophrenic patients; HC, healthy controls; D, depressive patients; PDA, panic disorder with agoraphobia; SP, social phobia; SRI, serotonin reuptake inhibitors.

Chapter 3. The study of memory functions in OCD

Similar contradictory results as in the case of executive functions exist in the domain of memory research regarding OCD. In this chapter of the dissertation we will focus on the key theoretical assumptions and research findings with relevance to the main thesis points: short term and PM respective on the role of inhibition in selective retrieval.

3.1. Short term verbal and visual memory

It seemed a reasonable explanation that in OCD behind repetitive thoughts and actions is a memory system failure (Sher, Frost, & Otto, 1983). The assessment of memory functions however revealed that these are mainly a secondary consequence of less effective organizational strategies and impaired executive functions (Savage, 1998). There are results also saying that OCD patients do not really trust in their own memories, and that there is a *metamemory deficit* (see Tuna, Tekcan, & Topcuoglu, 2005).

There is a consensus in literature that *verbal memory store and recall* is intact in OCD, while there is a deficit at the level of effective encoding strategy use (see Christensen et al., 1992; Deckersback et al., 2005). On encoding strategy the authors understand the way how the incoming information is grouped and encoded in the memory.

According to the literature the OCD group performs the Digit Span Forward Task (Aronowitz et al. 1994; Christensen et al., 1992; Okasha et al, 2000; Savage, Keuthen, & Jenike, 1996; Tallis, Pratt, & Jamani, 1999; Zielinski et al., 1991) and the Digit Backward Task (Cohen et al., 1996) at the level of the healthy control group, while there are results about significantly poorer performance on the Digit Span Forward task (Berthier et al., 1996). There were no differences on patient's performance on the Wechsler Memory Scale (Boone et al., 1991), on the Rey Auditory Verbal Learning Task (Zielinski et al., 1991) and on the Californian Learning Task (Christensen et al., 1992). OCD patients recall significantly fewer verbal, semantically related items then healthy control subjects probably because they don't spontaneously use verbal organizational strategies. These differences disappear if they are instructed explicitly to do so, which reflects that there is most probably an initiation rather than a lack of storage capacity problem (Deckersback et al., 2005).

The postulated strategy initiation deficit probably relies on the difficulties in detection of most relevant features of fast changing stimuli, but this assumption needs further research.

In contrast most of the studies found impaired performance in *visual and spatial memory* in OCD (see Aronowitz et al., 1994; Deckersbach et al., 2000; Moritz, Kloss, Jahn, Schick, & Hand 2003; Purcell, Maruff, Kyrios, & Pantelis, 1998; Zitterl et al., 2001).

OCD patients remember fewer items from the *Corsi-Block Tapping Task* than matched healthy control subjects (Moritz et al., 2003; Zitterl et al., 2001). It is one of the most well-known tasks used to asses short term spatial memory in which the examiner tapes the blocks from the apparatus in randomized sequences of increasing length and the subject's task is to reproduce each sequence immediately after presentation (see Figure 1).

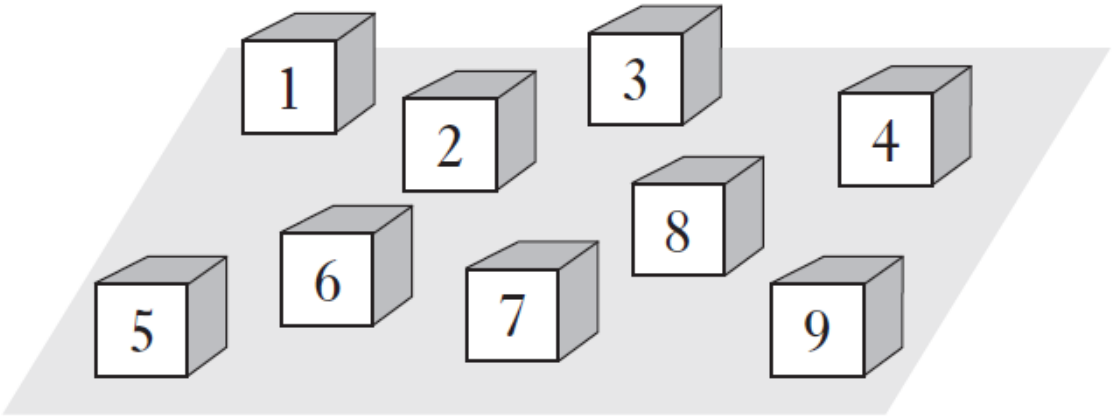

Figure 1. Corsi Block Tapping Task

On The *Rey Complex Figure Task* which is most often used as a visual short term memory as well as visual episodic memory test OCD patients perform at the level of healthy controls at the copy phase, but show impairment in the instant and delayed recall phases (Martinot et al., 1990; Penades et al; 2005) which was interpreted also in the context of impaired organizational strategy use.

From all these results we can conclude that most researchers consider that visual spatial short term memory is impaired in OCD due most probably to impaired organizational strategies used during the encoding phase.

3.2. Prospective memory (PM)

PM refers to the encoding, storage, and retrieval of delayed intentions (Ellis, 1996; Einstein & McDaniel, 1996) and it has different phases, such as formation, retention, initiation, execution and evaluation of intentions (Kliegel, Martin, McDaniel, & Einstein, 2002). In this multiple phase outline of PM process, intention formation refers to the point when intention is formed and encoded, intention retention to the period when intention is maintained in long term memory, and the ongoing activity (-ies) take place, intention initiation to the period in time when the actual intention is (or supposed to be) initiated and intention execution to the phase when the intention is realized according to the previous plan (Kliegel, Martin, McDaniel, & Einstein, 2001).

The authors think that each phase can be matched with a specific dominant cognitive function and proposed an explanatory model (see Figure 2). According to this view, intention formation, initiation and execution involves specific executive components associated mainly with frontal networks, while intention retention, which requires the retrospective component depends mainly on hippocampal structures.

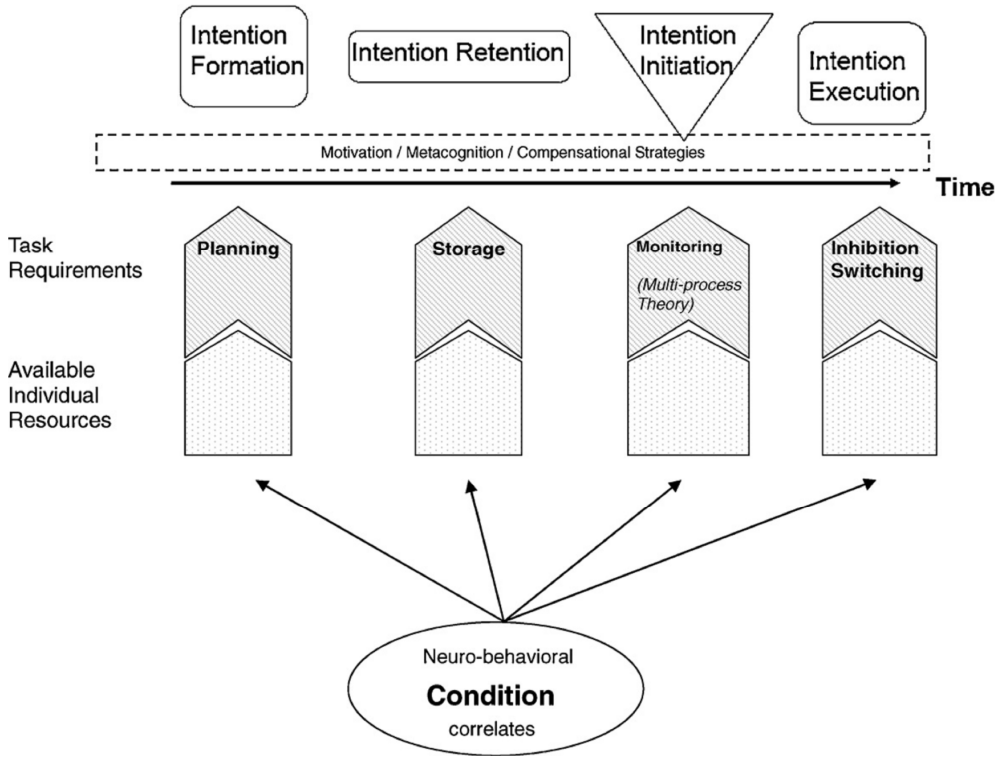

Figure 2. Process model of PM and associated neuro-cognitive mechanism (Kliegel, Altgassen, Hering, & Rose, 2011)

Four dominant dimensions have been used in the literature to classify PM tasks. The first classification distinguishes between *event* and *time based* PM tasks (Einstein & McDaniel, 1996). In event-based tasks the PM cue which signals the execution of the intended action is an externally presented event (e.g., the entrance of the experimenter in the room, the appearance of a form on the computer display). In time-based tasks the intended actions supposed to be carried out at a well specified point in time (e.g., call me at 8.p.m.; press the up-arrow key after four minutes).

The second dimension is the complexity of the PM task, and distinguishes between *simple, single intention* tasks which require subject to execute an intended action just once (e.g., the 2 PM subtests in the Rivermead Behavioural Memory Test (RBMT), Wilson, Cockburn & Baddeley, 1985) and *complex, multi intention* tasks which require to plan and carry out several delayed intentions (e.g., Six Elements Task from the Behavioural Assesment of Dysexecutive Syndrome (BADS), Wilson, Alderman, Burgess, Emslie, & Evans, 1996; the Virtual Week task, Rendell & Craick, 2000).

The third dimension refers to the context – environment of the PM task and distinguishes between *laboratory* (e.g., press a button if situations) and more *naturalistic*, every day life situation tasks (e.g., buy groceries on a way back home) (Henry, MacLeod, Phillips, & Crawford, 2004; Phillips, Henry, & Martin, 2008).

The fourth dimension is the agent who forms the intentions to be carried out, creating *self cued* (e.g., at 9 a.m. I will call X) and *cued by others* or by the *environment* (e.g., my boss told me to call X at 9 a.m.) PM tasks.

These dimensions are applied a little bit arbitrary and serve just as guidelines for defining different type of PM tasks but in our daily life and in experimental settings we usually face a combination of all these (e.g., press the up-arrow key in every 2 minutes while you are performing a general quiz – self cued laboratory complex time based PM task).

3.2.1. Theories of PM – monitoring as a key component

In the theories of PM developed in the last two decades, monitoring is described as a strategic process. Below, the most important theories from this field of research pointing out the role of monitoring processes are outlined. The earliest theoretical approach accounting for PM retrieval in the context of other ongoing behaviors is probably the SAS model (Burgess & Shallice, 1997; Norman & Shallice, 1986) described in the previous chapter.

The multiprocess model

This model proposes that although PM is supported by automatic processes when there is a strong association between the PM target event and the intended actions, there are other circumstances when PM performance is mediated by more strategic monitoring processes (Einstein et al., 2005; McDaniel & Einstein, 2000; McDaniel, Guynn, Einstein and Breneiser, 2004).

The multiprocess framework makes a distinction between focal and nonfocal cues. The previous refers to the PM cues which overlap with the information relevant to performing the ongoing task, while the second to those cues which are part of the environment but not considered by the subject (McDaniel, Einstein & Rendell, 2008). According to this approach focal cues can stimulate automatic spontaneous retrieval of the intended action while nonfocal cues require more strategic attentional resources (Einstein et al., 2005).

Monitoring is one of the possible strategic processes which indicate when it is appropriate to execute an intended action. There are situations when monitoring is more important than in others, for example when the PM target events are not salient, or there is no strong association between target events and the intended action, or when the ongoing activity does not elicit focal processing of target events. It is also believed that monitoring for targets plays a specific role in individual's behaviors with obsessive-compulsive tendencies.

The preparatory attentional and memory processes model (PAM)

The model proposes that non-automatic attentional processes are always involved in PM retrieval (Smith, 2003; Smith & Bayen, 2004). One component of these preparatory attentional processes is monitoring for the PM target events that indicate the appropriate time

for PM actions. There are situations when we need to be prepared in some way for the potential occurrence of the target to be able to perceive it (Smith, 2003).

The PAM theory argues that for an intention to be executed we have to devote some amount of our limited cognitive capacity to make decisions about how to respond to the environment around us and it refers to these as preparatory attentional processes. These processes prepare us for the return of the intended action to the focus of attention and are required during the performance interval (Smith, 2008). For example if we must remember to buy a book on the way back home, we must engage in preparatory processing during the interval when the opportunity to stop at a bookstore is possible but not during the whole day.

The amount of available cognitive capacity and the capacity devoted to the ongoing activity influences the probability that an intention be completed and beside these according to the theory it can be said that successful PM also involves correctly recognizing the target events and recalling the intended actions (Smith, 2008). The core difference between the multiprocess framework (McDaniel & Einstein, 2000) and PAM theory is that the latter proposes that PM tasks for successful performance will always require resource-demanding preparatory processes, while the multiprocess framework states that there are cases when intentions are automatically retrieved.

Theory of monitoring

There is a recent concept that proposes that monitoring comprises two processes that demand resources: instantiating a PM retrieval mode and making periodic checks of the environment for an appropriate target to execute the intended action (Guynn, 2008). The retrieval mode concept refers to the mental set from the retrospective memory literature which is required by the attempt to retrieve information independent from its success or failure (see Tulving, 1983; 2002).

There is a vast amount of data from cognitive neuroscience studies (fMRI, PET, ERP) supporting a specific right frontal activation pattern when subjects try to remember information from their past indifferent from its success (McIntosh, Nyberg, Bookstein, & Tulving, 1997; Nyberg et al., 1995; Rugg, Fletcher, Frith, Frackowiak, & Dolna, 1997).

In PM research retrieval mode is also conceptualized as a task set to treat stimuli as cues to retrieve stored intentions (Guynn, 2008). Retrieval mode is a more continuous while target checking a more periodic process. The two component theory was elaborated in the context of event based PM, but may also apply to time-based PM.

According to Guynn (2008) retrieval mode is a necessary component of monitoring while target checking is not and it is not even always necessary. According to this view when PM retrieval is guided by monitoring, either the two components – the retrieval mode and target checking – or just the retrieval mode could be involved. Results from past experiments (Guynn, 2001, 2003, 2005) support this view but without clear double dissociation evidences.

Based on these advances, PM research produced dependent measures that were developed to analyze the role of monitoring functions in PM responses. These measures are the accuracy and latency of the ongoing activities in which the PM task is embedded (Guynn, 2003; Kliegel, Martin, McDaniel, & Einstein, 2001; Kliegel, Martin, McDaniel, & Einstein, 2004).

The principal way to measure monitoring in an event-based PM task is to compare the performance on an ongoing task, during which PM instructions or targets are embedded (experimental trials), with the performance on the same task when no PM instructions or cues are assigned (control trial) (Guynn, 2008). The lower accuracies or higher latencies on the experimental trials relative to the control trials provide evidence of monitoring activity (Guynn, 2003; Kliegel et al., 2001; Kliegel et al., 2004; Marsh, Hicks, & Cook, 2005).

3.2.2. Main cortical structures and neuronal networks involved in PM – connections with OCD

The relationship between monitoring functions of PM cues and OCD symptoms is also interesting from the perspective of neuroimaging studies. A series of studies found evidence that the rostral prefrontal cortex (BA10) is involved in PM (Burgess, Quayle, & Frith, 2001; Burgess, Scott, & Frith, 2003; Simons, Schölvinck, Gilbert, Frith, & Burgess, 2006).

In a positron emission tomography (PET) study Burgess et al. (2001) demonstrated that different cortical areas are involved in the maintenance and realization of intentions. They found increased regional cerebral blood flow (rCBF) in the frontal pole bilaterally, in the right lateral prefrontal, inferior parietal cortex and the precuneus, and decreased rCBF in the insula in the left hemisphere when healthy participants maintained and realized an intention. In contrast, they found increased rCBF in the right thalamus and decreased rCBF in the right dorsolateral prefrontal cortex when subjects executed versus maintained an intention.

Putting these results together with attention theories Burgess and his colleagues (Burgess et al., 2003, Burgess, Simons, Dumontheil, & Gilbert, 2005; Burgess, Gilbert, & Dumontheil, 2007a, Burgess, Gilbert, & Dumontheil, 2007b) outlined the ***'gateway hypothesis'*** which makes a distinction between *stimulus-oriented* (SO) and *stimulus-independent* attending (SI) (McGuire, Paulesu, Frackowiak, & Frith, 1996). The former is involved in the processing of the present sensory input, while the latter is required in the realization of self-generated or self-maintained thoughts. According to the hypothesis SO attending is supported by the medial rostral PFC while SI cognition by the lateral rostral PFC which means that the former is mainly involved in suppressing internally generated thoughts while the latter in intention maintenance (Burgess, Gilbert, & Dumontheil, 2007c).

We think that OCD patients might have difficulties in SI attending, which has also a negative effect to the SO attending. It is possible that in OCD the maintenance of the intention requires extra SI attentional processes, which impairs the execution of the ongoing activities (SO attending).

On the other a hand there is evidence that PM is more sensitive to executive functions deficits than to retrospective storage impairments (Kliegel et al., 2004; Kopp & Thone-Otto, 2003). This pattern of findings supports the idea that PM may more strongly rely on prefrontally mediated (executive control) processes than on temporally mediated (retrospective memory) processes (Brunfaut, Vanoverberghe, & d'Ydewalle, 2000; McDaniel, Glisky, Rubin, Guynn, & Routhieaux, 1999). Specific subprocesses of PM – as planning of an

intention or the initiation and execution of an intention which requires executive control mechanism – rely on the prefrontal cortex while others as the retrieval of the intention content, essential for the retrospective component of PM on the medial temporal lobe (Cohen & Reilly, 1996; Guynn, McDaniel & Einstei, 2001).

As it has been outlined in the previous chapter of the dissertation, the primary cognitive deficit contributing to the OCD neuropsychological profile is the dysfunction of the executive system (Olley et al., 2007). The neuroimaging research of OCD gave a further hint that PM functions could be relevant in an OCD endophenotype, as it was found that those brain areas that are involved in PM are among the affected brain structures in OCD.

Although there is evidence of the altered function of the fronto-striato-pallido-thalamico pathways (Saxena, Brody, Schwartz, & Baxter, 1998; Saxena & Rauch, 2000), the most consistent findings came from structural neuroimaging showing that the volume of the orbitofrontal cortex is significantly reduced (Atmaca, Yildirim, Ozdemir, Tezcan, & Poyraz, 2007; Choi et al., 2004; Kang et al., 2004; Szeszko et al., 1999), while there is a volumetric increase of the thalamus in OCD (Atmaca et al., 2006; Gilbert et al., 2000). The thalamus is involved in the anticipatory attentional processes and in the monitoring of self-generated actions (Blakemore, Rees, & Frith, 1998; Portas et al., 1995). Symptom provocation studies with PET and functional magnetic resonance imaging (fMRI) find increased rCBF and stronger activity bilaterally at the orbitofrontal cortex, at the right nucleus caudatus and at the left anterior cingulate cortex (Breiter et al., 1996; Rauch et al., 1994).

It can be argued that over-activated PM intentions in OCD go together with a response inhibition deficit, and these two factors together contribute to the higher rate of false alarms in event based PM task (see Study 3). This interpretation fits well with the neurobiological theories of OCD, where this disorder is perceived as a result of the serotonergic system hypofunction (Hasselbach et al., 2007; Stengler-Wenzke, Muller, & Angermeyer, 2004), which has less effective inhibition on connections to basal ganglions and prefrontal cortex dopaminergic pathways, causing a hyperactivity of the dopaminergic system (for a review in Hungarian see Harsányi, Csigó, Demeter & Németh, 2007; Kim, Koo, & Cheon, 2003; Marraziti, Hollander, & Lensi, 1992; van der Wee, Stevens, & Hardeman, 2004).

This connection of the two predominant neurotransmitter systems affected in OCD can be one of the reasons that the SSRIs have limited success in the treatment of OCD symptoms. In recent studies, the treatment of SSRI non-responder subgroup of OCD patients was supplemented by antipsychotics with dopaminergic activity. Many studies have confirmed the beneficial effect of these antidopaminergic substances on the hyperactive cortico-striato-

thalamic loops in OCD (Bloch, Landeros-Weisenberger, & Kelmendi, 2006; McDougle, Goodman, & Price 1990; Metin, Yazici, Tot, &Yazici, 2003).

Considering all these findings together, there is some evidence that those brain networks which take part in the realization of PM functions are affected in OCD.

3.2.3. Studying PM in OCD

While at the beginning of PM research the focus was on the outline, description of main differences between retrospective memory (Einstein & McDaniel, 1990, 1996) and PM or on the developmental aspects of prospective remembering (Kliegel, Jäger, & Phillips, 2008) today a move toward the clinical field concentrating mainly on the impairments is experienced. There is a considerable amount of result with different disorders as schizophrenia, Parkinson disease, Alzheimer's disease, patients with head injuries, with substance abuse and with developmental disorders (see Kliegel et al., 2008, 2011).

As far as we know there are just a few studies with OCD patients or with subclinical groups with dominant checking symptoms or obsessive tendencies in the domain of PM literature. Below, the main findings are summarized and the main hypothesis is outlined.

In one study using the Rivermead Behavioural Memory Test the authors found no significant difference between OCD patients and healthy controls on the PM score (Jelinek, Moritz, Heeren, & Naber, 2006). In a large heterogeneous clinical OCD sample Moritz, Kuelz, Jacobsen, Kloss, and Fricke (2006) found no evidence about subjective complains related to PM performance compared to a group with depression.

In three seminal studies Cuttler and Graf (2007, 2008, 2009) investigated PM functions of subclinical checkers and produced compelling evidence that checking compulsions are associated with lower performance in event and time based PM tasks. Higher checkers reported more everyday PM failures than low and medium checkers. They also found that depression and state and trait anxiety had no influence on PM performance and concluded that checking compulsions are compensatory reactions to experienced PM failures in the past. Their results support the theory that PM deficit contributes to the development and maintenance of checking compulsions. Subclinical checkers are aware of PM failures which induce concerns and an urge to recheck things.

Marsh, Jameson, Cook, Amir, & Hicks (2009) in a subclinical population examined the connection of PM retrieval with obsessive-compulsive tendencies (washing compulsions) using threat and neutral information as cues and found that while in case of neutral cues there was a PM impairment, then the threat related stimuli improved PM performance in this subclinical group. The extra attentional bias produced an extended processing of threat-related cues and this improved the subjects PM performance, helping them to overcome their natural deficits. These results are in line with previous findings that people with general anxiety disorder manifest severe attentional biases (Hayes and Hirsh, 2007) and subclinical group of

first year college student's event-based PM performance negatively correlated with the individual levels of anxiety (Harris and Menzies, 1999).

Another study found evidence (Harris, Vaccaro, Jones & Boots, 2010) supporting the event-based PM deficit in a clinical sample of OCD checkers. The patients in this study did not report more subjective PM errors and their confidence in PM accuracy was higher than that of control subjects which is inconsistent with the Cuttler and Graf previous findings with subclinical checkers (2007, 2008). The OCD checkers expressed greater confidence in event based PM task and predicted also that they will be more accurate on the time based PM task then controls. The later finding was interpreted by the availability of an extrinsic checking strategy. But they manifested impaired performance on the event based PM, showing that objective PM deficits can also occur in the absence of more complaints about PM failures (Harris et al., 2010).

Due to these results the hypothesis and theoretical explanation of Cuttler and Graff (2009) may need remediation. It seems that clinical OCD checkers have an inappropriate insight to their own PM abilities and therefore it is unlikely that their concern about PM failures is driving their checking behavior. Checking is a much more successful strategy in this phase of the disorder which helps avoiding PM failures, but the question is still open for future research, because it is still possible that checking has developed at the early stage as a response to the concerns about PM failures (Harris et al., 2010).

According to our view this heterogeneous clinical group could contribute to the filed of PM research with considerable results. In our studies answers were seeked to the following main questions:

- Is there an event-based PM impairment in OCD?
- Why is there a PM impairment in OCD?
- Can the findings from this specific population add something to the existing theoretical models?
- What are the therapeutical benefits of these findings?

We think that after intention execution, OCD patients have difficulties cancelling successful activities, which rely on inhibition deficit. We also think that in OCD the PM system is in an overactivated state, which manifests at the behavioral level in an over-monitoring activity for PM cues.

3.2.4. A possible PM model of OCD

Our approach tries to find connection points between PM research, goal attainment, attention systems and the neurobiology of OCD. The picture is very complex, therefore only the main points will be outlined and it is believed that this theoretical ideas needs further development and research support.

We think that another step could be also important in the process model of PM (Kliegel et al., 2011), what we have called the *cancellation phase*. It refers to the mechanism that after realizing an intention and the system gets positive feedback will stop the successful action (see Figure 3). Otherwise the intentions would remain in an overactivated state and would cause persistent thoughts and actions in the PM system. This component relies strongly on inhibition processes. OCD patients following the successful execution of a specific PM action may not cancel the activation of this action representation and this results in a constant search for environmental PM cues and in the appearance of the false alarm type errors (responding to a PM cue, when not supposed to).

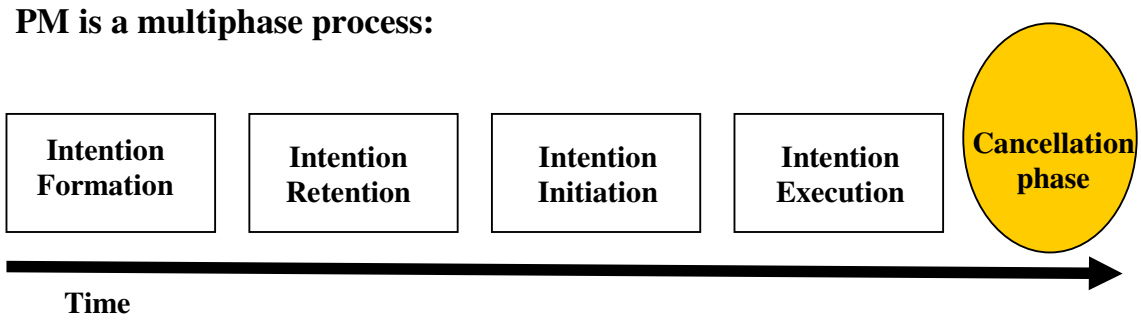

Figure 3. The modified process model of PM

Goal attainment like prospective and executive system also involves attentional mechanism and relies strongly on the reward system. For an adaptive behavior we also need our cognitive system to be able to perceive and successfully analyze the reward and punishments signals and redirect our behavior toward the next coming goal. Reaching a goal is a sign for attention networks that this behavioral shift is possible. This mechanism

according to recent studies could be mediated by the phasic activation of locus coeruleus (LC) (Aston-Jones & Cohen, 2005; Bouret & Sara, 2005). We know that in OCD beside the serotonerg and dopamninerg systems (e.g., Denys, Van Der Wee, Van Megan, & Westenberg, 2003; McDougle et al., 1990) the noradrenerg system is also affected (e.g., Brambilla, Barale, Caverzasi & Soares, 1997). It is presumed that the transmission of noradrenalin is increased from the LC to the frontal cortex, thalamus, hypothalamus and limbic system compared to normal subjects (Brambilla et al., 1997; Hollander et al., 1991).

There is evidence also supporting the hypo- (e.g., Chamberlain et al., 2008) respective hyperactivity of the OFC (e.g. Rauch et al., 2007) and the hyperactivity of the anterior cingular cortex (e.g. Maltby et al., 2005). These structures play important roles in evaluating reward and costs and there is a growing amount of evidence that LC receives its most prominent descending cortical projections from these frontal structures determining its working mode (Aston-Jones & Cohen, 2005).

It can be argued that this neurobiological setting might contribute in OCD to the overactivity of intentions and to the deficit at the cancellation component in the PM system, determining the impaired performance in event-based PM tasks. There are a lot of open questions and further studies are needed to clarify these hypotheses.

3.3. The role of inhibition in selective retrieval

Sometimes we wish our memory have an unlimited storage capacity but hopefully it is not the case, and we can be thankful to forgetting, which in many cases can be adaptive. According to James (1980, p. 680), "If we remembered everything, we should on most occasions be as ill off as if we remembered nothing". The mechanism which makes this adaptive form of forgetting possible is *inhibition* (Anderson, 2003; Bjork, Bjork & Anderson, 1998; Bjork, 1989). Bjork (1989, p. 324) defined inhibition as a: "suppression-type process directed at the to-be-inhibited information for some adaptive purpose."

We constantly learn new pieces of information and skills and this way we challenge our earlier established knowledge, which sometimes could be difficult to access or simply inaccessible because of inhibition. According to Anderson (2007, p. 2) inhibition refers to a mechanism that "acts upon a memory trace to induce a potentially reversible change in its state, making the trace less accessible".

Inhibition could explain why we forget previously studied items while we retrieve some items from memory, a phenomenon known as the *retrieval induced forgetting* (RIF, Anderson, Bjork, & Bjork, 1994). This phenomenon was often studied with the *retrieval induced paradigm* (Anderson, et al., 1994). In this paradigm subjects study a list of category pairs (e.g., vegetables - carrot; sports- cycling; profession - psychologist etc.) in the study phase, then during the practice phase they retrieve half of the exemplars from half of the categories by a category and two initial letter cues (e.g., vegetables – ca___; half of the vegetables). Practiced items are referred to as Rp+ (e.g., carrot), nonpracticed items from practiced categories as Rp- (e.g., cabbage; the other half of the vegetables), and items from nonpracticed categories as Nrp (e.g., psychologist). On the final test all of the studied and not only the practiced items are recalled.

The typical finding is that Rp+ items are better recalled while Rp- items worse then Nrp items (baseline). The lower recall of Rp- items compared to Nrp items is referred as the RIF and has been found in a wide range of circumstances (see Anderson & Bell, 2001; Anderson, 2003; Bajo, Gómez-Ariza, Fernandez, & Marful, 2006; Levy & Anderson, 2002; Levy, McVeigh, Marful, & Anderson, 2007; Storm, Bjork, & Bjork, 2005).

These findings suggest that selectively retrieving target items will involve inhibitory mechanism that suppresses competing items in memory. This account also assumes that inhibition is an active rather then a passive process, Rp- items are actively inhibited during the retrieval practice of Rp+ items and forgetting is the consequence of these inhibitory processes

that acts to resolve competition between target items during retrieval. It is also assumed that this inhibition reflects executive control mechanism (Storm, 2011).

The above findings on the other hand can be explained by interference mechanism (e.g., Camp, Pecher, & Schmidt, 2007). For example in the retrieval practice paradigm we can say that forgetting is caused by interference mechanism because the cue (e.g., vegetables) becomes stronger for the practiced item (e.g., carrot), while the associations between the cue and non-practiced items (e.g., cabbage) become weaker. According to this approach the emphasis is on the modified effectiveness of the cue to retrieve specific targets.

To distinguish between these two approaches the final memory test should use independent cues, cues which are not associated with the practiced items. This seems a reasonable criteria because Anderson (2003) states that the item itself is inhibited and not the relation between the target and its category. There are studies with evidence supporting the RIF effect by independent cues (e.g., Anderson & Spellman, 1995; Anderson, Green, & McCulloch, 2000; Johnson & Anderson, 2004;) and studies which failed to replicate the reported findings (e.g., Camp et al., 2007).

Another question refers to the duration of the RIF effect, and it has been found that it disappears after 24 hours (delayed testing) if the retrieval-practice phase followed immediately the encoding phase (MacLeod & Macrea, 2001), suggesting that it reflects a reversible change in state. Most of researchers consider the retrieval practice effect a short rather then a long term effect (Anderson, 2001; Saunders & MacLeod, 2002). Our study found evidence supporting the presence of this effect after 12 hours, if a nocturnal sleep occurred during the retention intervals (Racsmány, Conway & Demeter, 2010). According to the *episodic inhibition* account in the retrieval practice procedure the study phase gives rise to the formation of an episodic memory and the practice phase establishes a pattern of activation and inhibition over these contents. Then, during recall, this pattern of activation-inhibition will mediate the access to memories (Racsmány & Conway, 2006).

There were studies on RIF with different clinical populations (schizophrenia, Alzheimer disease, depression, brain damage) but as far as it is known, there are no studies involving OCD patients. It is important to consider that the study of OCD in this context can be with critical relevance in this area because it can produce relevant results considering the debate between the inhibitory and interference accounts, to the relation between executive functions and RIF and to the possible modulator effect of stress on RIF.

Further two recent results will be presented that should also be considered relevant from the aspect of OCD research.

Koessler, Engler, Riether and Kissler (2009) found evidence that psychosocial stress undermines the RIF effect in healthy subjects. In the stressed group retrieval practice did not impair the recall of RP- items and only this group shows an increase in the salivary cortisol level which reflects the hyperactivity of the hypothalamic-pituitary-adrenal axis, an increase in the state anxiety level and a decrease in the measure of social well-being.

From previous works it is known that stress negatively affects contextual binding of items to episodes (Payne, Nadel, Allen, Thomas, & Jacobs, 2002) and Koessler et al. (2009) results add to this that stress can temporary suspend the inhibitory mechanism which operates under RIF, and it seems that the hyperactivity of the hypothalamic-pituitary-adrenal axis plays an important role in the mediation of these processes.

Groome and Sterkaj (2010) found evidence that clinical depression reduces RIF scores which the authors interpreted from the point of view that depression could impair memory functions with inhibitory nature. On the other hand it is also possible that the impaired inhibitory functions might cause the intrusion of negative thoughts and memories making individuals more vulnerable.

Further research is needed to clarify the relationship between RIF, cognitive impairments and different clinical symptoms.

Chapter 4. Possible neuropsychological models of OCD

4.1. Hypothesized neuropsychological model of OCD

In an early hypothesized neuropsychological model of OCD - which offers plausable explanations for the neuropsychological findings even today - fronto-striatal dysfunction leads to impaired executive functioning, which manifests in: difficulty in appreciating the larger context, difficulty in prioritizing and planning behavior, difficulty initiating strategic action and difficulty in monitoring and shifting. These problems contribute to the observed clinical symptoms sustained and altered by the possible memory problems, which are a secondary result of the existing executive function deficits (see Figure 4; Savage, 1998; for a review in Hungarian see Demeter, 2010a).

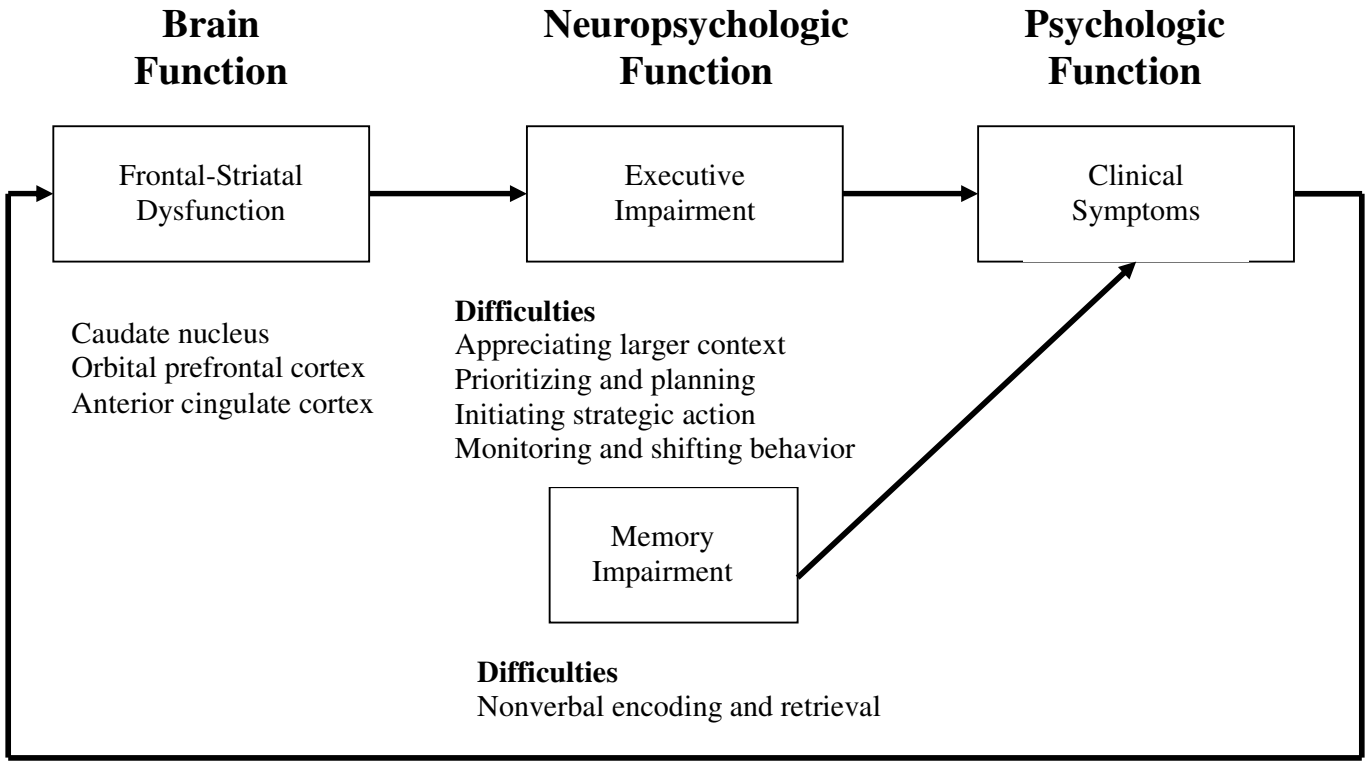

Figure 4. Hypothesized neuropsychological model of OCD (Savage, 1998)

The model was built on four important concepts: (1) in OCD the fronto-striatal impairment represents the primary brain dysfunction, (2) this dysfunction leads to primary executive impairment, and the nonverbal memory difficulties are a secondary consequence of

it, (3) the neuropsychological impairments have an impact on clinical symptoms of obsessions and compulsions, (4) the clinical symptoms feed back to the brain function.

According to Savage (1998) interpretation neuropsychological functioning appears as an intermediate level between brain dysfunction and clinical phenomenology. The model also describes a back route from the clinical symptoms toward brain functioning, creating a vicious circle. This way the obsessions and compulsions contribute to the altered brain functioning which supplies the maintenance of symptomatology. However, as a result of treatment the changes at the behavioral level can have a beneficial effect on brain functions. There are studies showing that modification at this level by medication or by psychotherapy produce stable changes at the neural level (e.g., Baxter et al., 1992; Baxter, 1994).

4.2. The failures of cognitive and behavioral inhibition processes

According to Chamberlain et al. (2005), not all aspects of the executive system are injured in OCD. The appearance of the relevant clinical symptoms and the main cognitive deficits – *inhibition of prepotent responses, set shifting and strategy use in memory probes* – could be explained by failures of cognitive and behavioral inhibition.

By *cognitive inhibition* the authors understand control over internal cognitions (e.g., intrusive thoughts or ideas) and by *behavioral inhibition* control over external motor activities (e.g., checking rituals). If different inhibitory mechanism could underlie different symptoms, then the neurocognitive indices of such inhibitory failures can be helpful in creating different subgroups. By this relatively reduced and simplified approach all the main neurocognitive findings of OCD can be explained by the impaired inhibition mechanism. The patients face problems in inhibiting prepotent responses (e.g., Go responses for NoGo trails), in set shifting (e.g., commit more preservative errors on the WCST) and in memory recall requiring extensive organizational strategy use (e.g., lifting already checked blocks on the CANTAB SWM) because of the inhibitory failures (see Figure 5).

Abnormalities at the level of the lateral orbitofrontal loop are possible candidates for the neurobiological basis of inhibitory dysfunctions as evidenced by lesion and functional neuroimaging studies (e.g., Aron, Robbins, & Poldrack, 2004; Bokura, Yamaguchi, & Kobayashi, 2001; Chudasama and Robbins, 2003; de Bruin, van Oyen, & Van de Poll, 1983).

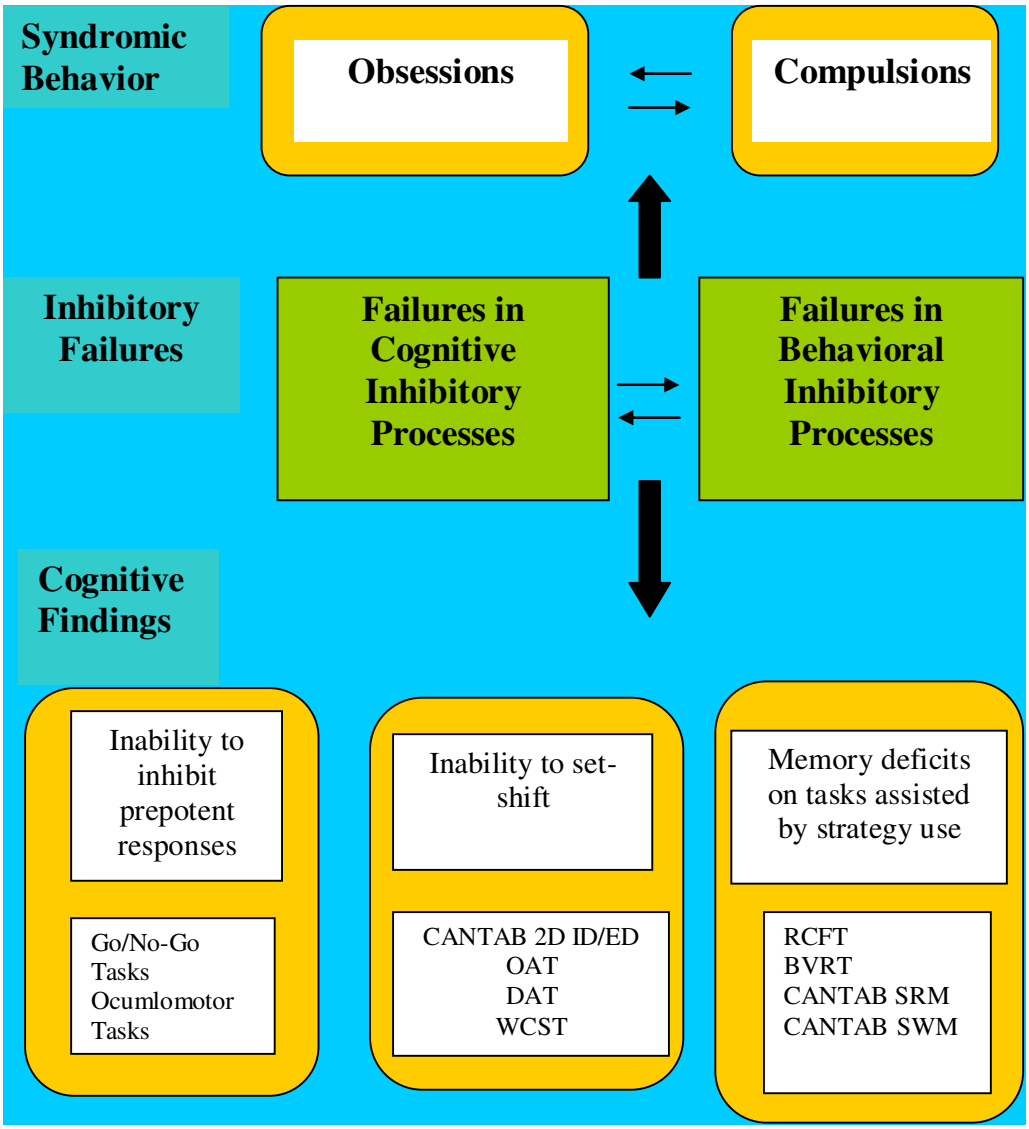

Figure 5. Failures in cognitive and behavioral inhibitory processes could explain many symptoms and cognitive deficits in OCD (Chamberlain, et al., 2005)

Note. CANTAB, Cambridge Neuropsychological Test Automated Battery; ID/ED, Intradimensional/Extradiemsional Set-Shifting Task; OAT, Object Alternation Test; DAT, Delayed Alternation Test; WCST, Wisconsin Card Sorting Test; RCFT, Rey Complex Figure Test; BVRT, Benton Visual Retention Test; CANTAB SRM, Cambridge Neuropsychological Test Automated Battery - Spatial Recognition Memory Task; CANTAB SRM, Cambridge Neuropsychological Test Automated Battery - Spatial Working Memory.

4.3. Current neurobiological model of OCD – beyond cortico-striato-thalamo-cortical pathways

Early neuroimaging studies have described the role of the cortico-striato-thalamo-cortical pathways in the pathophisology of OCD (see McGuire e al., 1994; Rauch et al., 2004; Saxena et al., 1998; Saxena & Rauch, 2000). There are 3 main circuits, or *"cortico-striatl loops"*: the so called affective circuit; the dorsal cognitive circuit and the ventral cognitive circuit (see Figure 6).

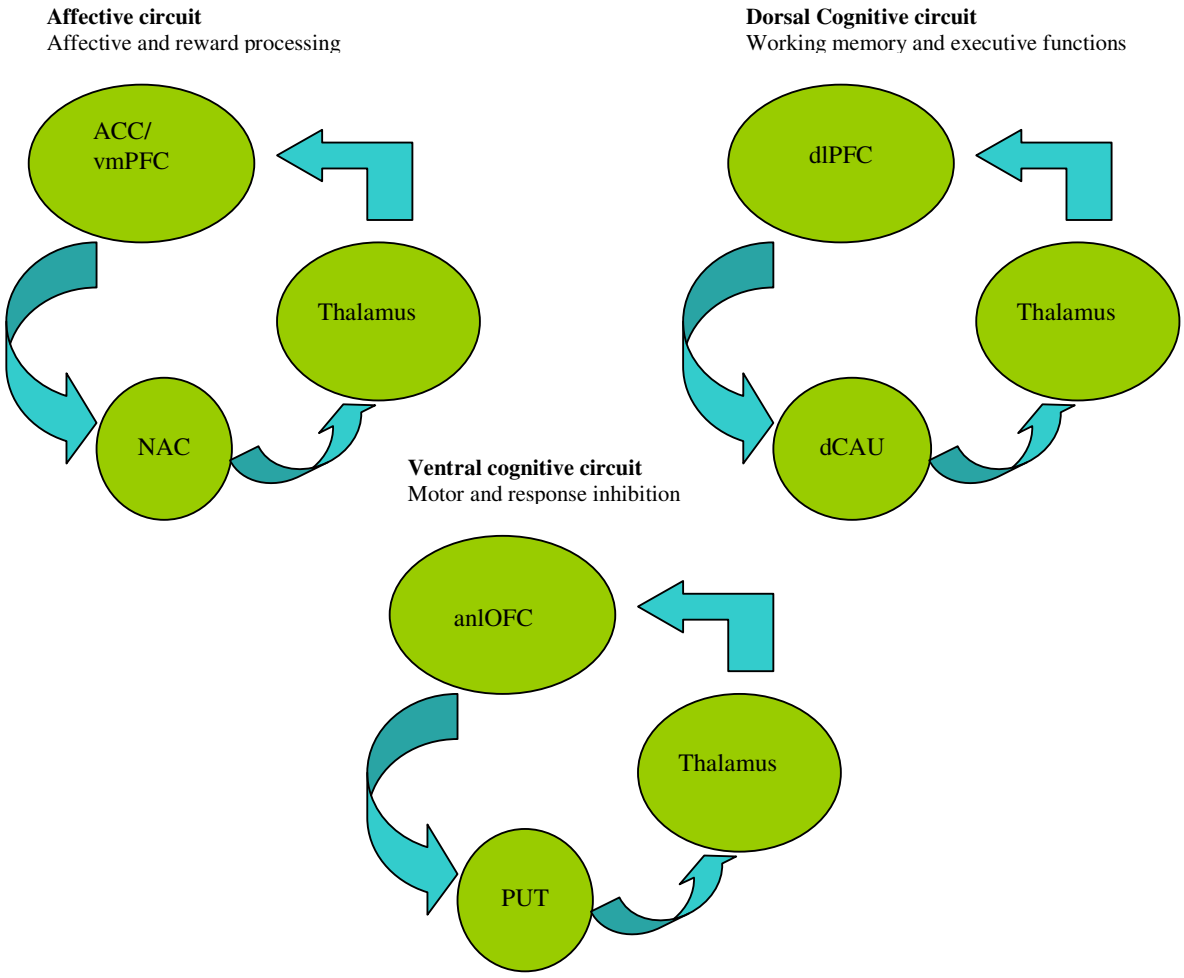

Figure 6. The cortico-striatal loops (Milad & Rauch, 2012)

Note. ACC, anterior cingular cortex; vmPFC, ventromedial prefrontal cortex; NAC, nucleus accumbens; dlPFC, dorsolateral prefrontal cortex; dCAU, dorsal caudatus; anlOFC, anterolateral orbitofrontal cortex; PUT, putamen.

The recent neuroimageing findings and neuropsychological implications in this area can be grouped in three main domains (Milad & Rauch, 2012):

The different role of lateral and medial orbitofrontal cortices (OFC) in reward processing and affect regulation

The lateral OFC is predominantly involved in the responses to punishment while the medial OFC seems to be more involved in reward processing (Elliott, Agnew, & Deakin, 2010; Kringelback & Rolls, 2004).

In OCD there is evidence supporting the hyperactivity of the lateral OFC and the hypoactivity of the medial OFC. Studies have found positive correlation between the severity of OCD symptoms and the hyperactivity of the lateral OFC (Adler et al., 2000; Rauch et al., 2007) and also near the inverse relationship between the hyperactivity of lateral OFC and treatment outcome (Rauch et al., 2007). On the other hand it seems that medial OFC activity correlates inversely with symptom severity (Rauch et al., 2007) and in this framework the anxiety faced in OCD could be the result of failure to activate the ventromedial prefrontal and OFC (Gilliam & Tollin, 2010).

There are studies which find opposing results (e.g., Chamberlain et al., 2008; Fitzgerald et al., 2005) to the above described dichotomy but regardless of the contradictory results it seems obvious that the dysfunction of two cortical areas plays different roles in the pathophisiology of OCD.

The role of dorsal anterior cingulated cortex (dACC) in error processing and fear expression

The dACC is involved in error detection and in all situations which implicate cognitive conflict resolution (Bush et al., 2002; van Veen & Carter, 2002).The paradigms most often used share the common properties that the subject must inhibit a prepotent or automatic response to produce the adequate one, as in the Stroop, Go-NoGo and antisaccade tasks.

There are studies with OCD patients showing the hyperactivity of the dACC in the incongruent compared to the congruent conditions (e.g., Fitzgerald et al., 2005; Maltby et al., 2005; Page et al., 2009). The dACC seems to a have a role in fear expression too (Milad et al., 2007). In therapy resistant patients the use of the anterior cingulotomy reduced the severity of the symptoms (Csigó et al., 2010; Dougherty et al., 2002) and successful SSRI treatment reduced the dACC metabolism (Perani et al., 1995). According to Milad and Rauch (2012) it could be that the hyperactivity of the dACC contributes to the persistence of error signals which produce the obsessive thoughts in OCD while on the other hand it is possible that this hyperactivity in OCD contributes to the observed fear and anxiety.

The role of amygdale in the expression and regulation of fear

Amygdala plays an important role in emotion processing (Davis & Whalen, 2001). In OCD pathophisiology the role of this cortical structure is incompletely understood, but there are studies demonstrating the hyperactivity of amygdala for OCD specific stimuli (Breiter et al., 1996; Mataix-Cols, et al., 2004).

Future research must try to integrate these entire neurobiological and neuropsychological findings toward an integrative model of OCD, contributing to the elaboration of different and more effective therapeutical methods.

Chapter 5. Main objectives and thesis points

In my thesis I concentrate on three main domains: executive functions, PM and retrieval inhibition.

We know from previous research that in OCD there is an executive function deficit, but its exact nature is still unclear, and the results are contradictory. Executive function is an umbrella term and during our studies we focus on two main components that we consider critical in OCD: set shifting and inhibition. We want to find and answer to the questions: "If there is an executive function impairment regarding these main components, how is its pattern of distribution in the clinically impaired ranges and how does the severity of symptoms relate to the different neuropsychological scores?"

As far as we know, we are the first group trying to connect executive impairment with PM function deficits in a clinical sample of OCD patients in a series of experimental studies. Our second main question refers to this topic: "Is there a PM deficit in OCD and if so how can we interpret the findings and connect them to symptomatology?" We hypothesize that OCD patients will manifest extra monitoring activity in an event-based PM task due to the overactivity of the PM system. This will result in increased reaction times in the ongoing tasks and more false alarm type errors on the PM task.

Our third guiding question group is related to the topic of memory retrieval using the retrieval practice procedure: "Is the RIF a short or a long term effect, and what factors modulate its persistence or diminishment?; "Is this effect present in OCD?"; "How is affected by symptom severity, working respective short term memory capacity and anxiety?". We hypothesize that if there is no active rehearsal the RIF effect will persist also after 12 hours and that sleep may play a critical role here. In OCD due to the described executive impairment we think that probably the automatic inhibition mechanism are also affected contributing in one hand to the lack of RIF effect. By a different point of view the diminished RIF effect could be attributed to the dysfunction of conflict detection processes observed in OCD.

5.1. Main goals

1. To assess the level of short-term memory and executive functions in OCD compared to healthy control subjects.
2. To describe the distribution of patients in different impairment ranges regarding short term memory, shifting and inhibition.
3. To clarify the relationship between symptom severity and cognitive impairments in OCD.
4. To demonstrate PM impairment in a series of event-based PM tasks compared to healthy control subjects.
5. To clarify the relationship between symptom severity, subjective evaluation of memory performance and error patterns during event-based PM tasks in OCD.
6. To demonstrate the long term effect of selective retrieval practice in normal population.
7. To compare OCD patients and normal subjects' performance in a modified retrieval practice paradigm.

5.2. Thesis points

We present the main thesis points together with the corresponding studies in parenthesis. The two published studies and the one accepted manuscript constitutes the core of the dissertation. They are presented in full length in the Studies section of the thesis. Study 3 and 5 are experiments not published yet in scientific journals. For these studies we present the methods, results, interpretation and conclusion under the Studies section and we integrate and discuss the main findings together with previous experiments under the Discussion and conclusion chapter.

Thesis I: Impaired executive functions in OCD (Study 1)[*]

OCD patients show impaired performance on the shifting and inhibition component of the executive system measured by the WCST respective Stroop Task. Patients with more severe symptoms committed significantly more perseverative errors on the WCST.

[*] For a detailed summary of executive functions and neuropsychological findings about OCD in Hungarian see Demeter et al., (2008) and Demeter (2010a) – publications related to Thesis I.

Thesis II: Impaired PM functions in OCD (Study 2 and Study 3)

OCD patients PM function is impaired compared to healthy subjects. PM instruction produced a significantly cost effect in OCD patients during the ongoing task due probably to an extra over-monitoring activity for PM cues.

OCD patients commit significantly more false alarm type errors in a modified event-based PM task compared to healthy controls probably due to an overactivity of the PM system and the desinhibition of the activated inadequate responses. The patients who consider their PM performance poorer commit significantly more false alarm type errors.

Thesis III: Long-term effects of retrieval practice (Study 4)

Retrieval practice effects were found to persist over a 12 hour retention interval when the items were maintained in memory by frequent rehearsal or when a period of nocturnal sleep occurred during the retention interval. When rehearsal was reduced or did not occur, long-term RIF was present only following a full period of sleep. It is proposed that consolidation processes occurring during sleep, possibly featuring off-line elaborative rehearsal, mediate this long-term effect of retrieval practice.

Thesis IV: No retrieval induced forgetting (RIF) in OCD (Study 5)[*]

OCD patients didn't show the RIF effect which could not be explained by working memory deficit or increased anxiety. The lack of RIF might be explained by the dysfunction of conflict detection processes observed in OCD.

[*] Publications related to Thesis IV: Demeter, Gy., Keresztes, A., Harsányi, A., Csigó, K., & Racsmány, M. (2012) and Demeter (2010b).

Chapter 6. Studies

6.1. Study 1: Impaired executive functions in OCD

Demeter, Gy., Racsmány, M., Csigó, K., Harsányi, A, Döme, L. & Németh, A. Intact short term memory and impaired executive functions in obsessive compulsive disorder. *Ideggyógyászati Szemle - Clinical Neuroscience* (accepted publication, 2012).

Intact short term memory and impaired executive functions in obsessive compulsive disorder

Abstract

Background and purpose: Previous neuropsychological studies produced inconsistent results with tasks tapping short-term verbal and visual-spatial memory and executive functions in obsessive compulsive disorder (OCD). The aim of this study was to investigate the presence of deficits in these cognitive domains. A further goal was to describe the distribution of patients in different impairment ranges for all functions, and clarify the relationship between symptom severity and cognitive impairments.

Methods: Thirty patients with OCD (DSM-IV) and 30 healthy volunteers were compared using well-known neuropsychological tasks. We assessed short-term verbal memory with the Digit Span Forward and Digit Span Backward Tasks, short-term visual-spatial memory with the Corsi Block Tapping Task, while we measured the level of executive functions with the StroopTask and the Wisconsin Card Sorting Test (WCST).

Results: Compared with a matched healthy control group, the performance of OCD patients was in the impaired range only in the two executive tasks. We find a significant positive correlations between the Y-BOCS (Yale-Brown Obsessive Compulsive Scale) total scores and the number of perseverative responses ($r(28) = 0.409$, $p < 0.05$) and perseverative errors ($r(28) = 0.385$, $p < 0.05$) in the WCST.

Conclusion: Our results gave evidence that executive functions are impaired while short-term memory is intact in OCD. This is in line with neuropsychological model of OCD that the deficit of cognitive and behavioral inhibition are responsible for the main cognitive findings of this disorder, most prevalently the deficit in set shifting and prepotent response inhibition.
Keywords: executive function, inhibition, neurocognitive deficit, obsessive-compulsive disorder, short term memory

INTRODUCTION

Obsessive-compulsive disorder is a highly debilitating neuropsychiatric condition characterized by intrusive unwanted thoughts and/or repetitive, compulsive behaviours, or mental rituals. [1] Recent research has produced compelling evidence for orbitofrontal- and basal ganglia-related neuropsychological dysfunctions. [2-5] According to recent findings the primary cognitive deficit contributing to the OCD profile is dysfunction of the executive system. [6] However, many studies have found less impaired or intact performance in traditional executive neuropsychological tasks for OCD patients. [7-10] The executive system is not unitary and different researchers understand different cognitive mechanisms on it. [11-13] The picture is more confusing if we take into consideration that the different methods used to evaluate executive functions require different cognitive processes. According to Miyake *et al.*[14] traditional neuropsychological executive tasks depend on three main central executive components: inhibition, modality-specific updating/monitoring and shifting. Inhibition here refers to one's ability to deliberately inhibit dominant, automatic, or prepotent responses when necessary. One of the most commonly used tasks to investigate inhibitory processes in OCD patients is the Stroop Task, in which subjects have to inhibit a dominant response (i.e. reading the name of the colour as written) and produce an adequate response (i.e. naming the ink colour). The results of this task with OCD patients are contradictory. Some studies have found

impairment in this task[15] and others have reported a similar performance by a matched healthy control group. [16-18] These differences could reflect the different methodology used and the heterogeneity of the OCD population.

Updating and monitoring in Miyake and his colleauges' model refers to refreshing the content of the working memory. [14] Maintenance of task-relevant information is accomplished by monitoring and coding relevant incoming information, and replacing old information that is no longer task-relevant. [19] Updating refers to the active manipulation of the content of working memory [14]. The tasks that are most commonly used to test this function in the OCD literature are the Letter Fluency Task[15], the Letter Memory Task[19], and the N-back Task. [20] The OCD patient performs poorly in the latter two tasks. There are a number of studies that shows that working memory is impaired in OCD, and is associated with symptom severity, and more importantly improves with treatment and is associated to frontal-striatal-thalamic activation. [21-23]

The third component of the executive system is shifting, which is responsible for coordinating the change between relevant and irrelevant sets. [14] The task that is most often used to study the set-shifting abilities of OCD patients is the Wisconsin Card Sorting Task (WCST). [24] Some studies have described set-shifting deficits in OCD using the WCST[25,26], while others have not. [27-30] WCST is a complex task and depending on the structural equation modeling analyses used it mainly reflects the shifting component of the executive system. [14]

Only a few studies have reported deficits in both verbal and spatial short-term memory, but most of the studies have failed to find verbal memory deficit in OCD. [8] OCD group seem to perform in the Digit Span Forward and backward task at the level of the healthy control group.[17,26,31-34] Most of the studies reported poor performance for OCD in tasks involving spatial working memory functions. [21,35-37]

The aim of the present study was to assess the level of short-term memory and executive functions in OCD compared to healthy control subjects. A further goal was to describe the distribution of patients in different impairment ranges for all functions, and clarify the relationship between symptom severity and cognitive impairments.

METHODS

Sample

Thirty patients diagnosed with OCD who satisfied the diagnostic criteria in the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV)[1] were examined at the Nyírő Gyula Hospital, Psychiatry II, Budapest, Hungary. A psychiatrist confirmed the diagnosis following the Structural Clinical Interview for DSM-IV Axis I Disorders (SCID-I). [38] The severity of OCD symptomatology was assessed using the Yale Brown Obsessive-Compulsive Scale (Y-BOCS). [39,40] We excluded subjects who met the criteria for severe depression and who had histories of alcohol/substance abuse or neurological disorder, and subjects with any concurrent comorbidity or lifetime history of schizophrenia and tic disorders. With regards medication, five patients had been unmedicated for at least 3 months, seven were taking selective serotonin reuptake inhibitors (four citalopram, three sertraline), twelve were taking double action noradrenaline and serotonin agents (seven clomipramine, four venlafaxine, one duloxetine) and one was taking a dopaminergic agent (amfebutamone). Thirty healthy volunteers were selected for the control group, which was matched according to age and education to the OCD group. None of the control subjects had a history of neuropsychiatric illness or were taking psychopharmacological medication. The research project has been approved by the Ethics Committee of the Budapest University of Technology and Economics. Written informed consent was obtained prior to the study (see Table 1).

Procedure

All OCD patients received the following evaluations: a psychiatric interview by an experienced clinician (M.D.); an assessment by trained raters that included the Structured Clinical Interview for DSM-IV to confirm current Axis I DSM-IV disorders[38], the Y-BOCS[39,40], the Hamilton Rating Scale for Depression (HAM-D, 21-item)[41,42], and a neuropsychological assessment performed by a trained neuropsychologist.

Table 1

Clinical and demographic characteristics of participants

Characteristics	OCD (*n*=30)		Healthy Control (*n*=30)	
	Mean	S.D.	Mean	S.D.
Age (years)	32.43	10.88	33.00	12.15
Education (years)	13.66	1.82	14.13	2.47
Sex (M/F)	14/16		14/16	
Y-BOCS Total	26.16	5.7		
Y-BOCS ORS	13.03	3.4		
Y-BOCS CRS	13.03	5.2		
HAM-D	10.56	6.16		

Note. OCD, obsessive-compulsive disorder; M, male; F, female; Y-BOCS Total, Yale Brown Obsessive Compulsive Scale Total score; Y-BOCS ORS, Yale Brown Obsessive Compulsive Scale, Obsessions-Severity Score; Y-BOCS CRS, Yale Brown Obsessive Compulsive Scale, Compulsions Severity Score; HAM-D, Hamilton Depressive Rating Scale; n.s., not significant.

Assessment of short term memory and executive functions

The neuropsychological test battery was designed to assess short-term verbal-, visual-spatial memory and executive functions.

Digit Span Forward and Digit Span Backward

We used the Digit Span Forward and Digit Span Backward Tasks as measures of verbal short-term memory. In both tasks trials consisting of a series of increasing numbers are presented orally by the examiner at a rate of one digit per second, and have to be repeated by the subject in the same (forward span) or in the reverse order (backward span). These tasks were mainly administered to OCD patients as part of the Wechsler Adult Intelligence Scale – Revised in earlier studies, in contrast, we have followed a more rigorous performance evaluation. Each trial consisted of four series of equal length, and we considered a trial completed if the subject reproduced at least two correct series. The number of correctly recalled trials for forward and backward span was counted. [43]

Corsi Block Tapping Task

This has been used for a variety of purposes, including the assessment of deficits in short-term non-verbal memory[44-46], investigating developmental changes and gender differences in spatial skills[47-49], and more recently, for clarifying theoretical conceptions of visual-spatial memory. [50]

We used the original Corsi apparatus and placement to measure the capacity of the visual-short term memory, which consisted of nine, irregularly arranged, 2.5 cm blocks. [51] The examiner tapped the blocks in randomized sequences of increasing length. The subject's task was to reproduce each sequence immediately after presentation. Our trials consisted of four

series of equal length, and we considered a trial completed if the subject reproduced at least two correct series. The number of correctly recalled trials for visual-spatial span was counted.

Stroop Colour Word Interference Test

This task measures the inhibition component of the executive system. [14] In part 1 the subject has to name the appropriate colour (red, green, blue or yellow) of printed Xs, and to press the designated answer key on a keyboard as quickly as possible. In part 2 the subjects have to read the names of colours printed in black ink and press the appropriate answer key. In part 3, the colour names are printed in incongruent ink colours, and the subject's task is to name the colour of the ink and press the correct answer key instead of reading the name. In this created interference situation the subject is required to inhibit a prepotent response in favour of an unusual one. We measured the reaction time and the errors committed in the three parts of the test. Following the presentation of the task a practice trial was employed to ascertain that the subject understood the task. The items remained visible on the computer screen until the subject pressed one of the possible answer keys. A total of 90 items were grouped into two blocks. There were 15 items in each block as printed coloured Xs, 15 items as colour names printed in black ink, and 15 items as colour names printed in different colours.

Wisconsin Card Sorting Test (WCST)

The WCST is one of the most frequently used neuropsychological tests of executive functions. [24] The correct resolution of the test invokes abilities such as: abstract reasoning, concept formation, decision-making, set shifting, and planning of behaviour. According to Miyake *et al.*[14] structural equation modeling (SEM) analysis, this complex task taps the executive functioning related to shifting.

We administered a computerized version of the test (WCST computer version 4, Research Edition) using the standard instructions.

RESULTS

Statistical analysis

The data were tested for normative distribution using the Shapiro–Wilk test and this analysis revealed that neuropsychological variables were not normatively distributed, and therefore the Mann-Whitney U non-parametric test was carried out. The correction for planned group comparisons is based on the domain-wise Bonferroni adjusted p value; with 2 domains (short term memory, executive functions) the p value required for significance is 0.025 (0.05/2). [21] Values < 0.05 were considered as trend towards significance. Pearson's correlation analysis was employed to examine the relationship between the scores on neuropsychological tests and symptom severity. All the reported p values are two-tailed except that reported for error inhibition index, which is one-tailed.

Results

OCD patients performed similarly to the healthy controls in the Digit Span Forward (DSF) ($z=-.86$, $p>0.05$, $r=0.11$) and Digit Span Backward (DSB) ($z=-.56$, $p>0.05$, $r=0.07$) tests. In the Corsi Block Tapping Task (CBTT) the OCD group completed significantly fewer series than the healthy control group ($z=-2.23$, $p=0.026$, $r=0.28$). Patients performed more poorly in the Stroop Task, were significantly slower in the colour naming condition (SRTC) ($z=-3.65$, $p<0.001$, $r=0.47$), in the colour reading condition (SRTR) ($z=-3.5$, $p<0.001$, $r=0.45$) and in the interference condition (SRTI) ($z=-2.98$, $p<0.01$, $r=0.38$). It is important to highlight that the OCD group committed higher number of errors in the interference condition (SEI), although this was only a tendency like effect ($z=-2.11$, $p=0.035$, $r=0.27$). We also calculated the so-

called *error inhibition index* (SEII) (Errors Interference Condition – Errors Colour Naming Condition), and there was a tendency like difference between the two groups, the OCD group achieving higher score (z=-1.59, p=0.05, r=0.2).

OCD patients committed a higher number of total errors in the WCST (WCST-TE) (z=-3.25, p<0.01, r=0.41), showed more perseverative (WCST-PE) (z=-3.1, p<0.01, r=0.41) and non-perseverative errors (WCST-NE) (z=-2.9, p<0.01, r=0.37), more trails were administered (WCST-TA) (z=-3.23, p<0.01, r=0.41), completed fewer categories (WCST-CN) (z=-2.83, p<0.01, r=0.36), required more trials to complete the first category (WCST-NT) (z=-2.24, p=0.024, r=0.28) and committed more failures in order to maintain a set (WCST-LS) (z=-2,33 p=0.02, r=0.3) compared to healthy controls. The main findings on short term memory and executive function tasks are summarized in Table 2.

Analysis of the relations between the Y-BOCS scores and the neuropsychological results revealed significant positive correlations between the Y-BOCS total scores and the number of perseverative responses ($r(28) = 0.409$, $p< 0.05$) and perseverative errors ($r(28) = 0.385$, $p< 0.05$) in the WCST.

Average differences are not the most informative data for any cognitive impairment in such a heterogeneous disorder as OCD, due to the large numbers of outliers. Therefore, we analyzed the percent of OCD patients performed within one standard deviation (normal performance), within (moderately impaired), and above (seriously impaired) two standard deviation of the average healthy adult group scores. This analysis revealed that merely the scores of executive tasks are in the severely impaired range (see Table 3).

Table 2

Results of short-term memory and executive tasks in the two groups

	OCD (n=30)		Healthy Control (n=30)		Test of independence	Significance	Effect size
	Median	Percentiles (25^{th}-75^{th})	Median	Percentiles (25^{th}-75^{th})	Mann-Whitney U test	p	r
DSF	6	5.75-7	6.5	6-7	U = 394.5 z = -.86	n.s.	0.11
DSB	5	4-5	5	4-6	U = 414 z = -.56	n.s.	0.07
CBTT	5	4-6	5	5-6	U = 308 z = -2.23	0.026	0.28
SER	0	0-0	0	0-0	U = 434.5 z = -.6	n.s.	0.07
SEC	0	0-0	0	0-0	U = 360 z = -2.55	n.s.	0.32
SEI	0.5	0-2.25	0	0-1	U = 324 z = -2.11	0.035	0.27
SRTR	1308	1166.75-1557.25	1025	948.75-1154.25	U = 213 z = -3.5	0.000	0.45
SRTC	1251.5	1023-1381	940.5	881.75-1092.75	U = 203 z = -3.65	0.000	0.47
SRTI	1580	1344.25-2019.75	1196	1059.5-1425.25	U = 248 z = -2.98	0.002	0.38
WCST-TA	112	81.25-128	75.5	70-92.5	U = 233.5 z = -3.23	0.001	0.41
WCST-TE	26	13.5-48.75	9.5	8-21.25	U = 230 z = -3.25	0.001	0.41
WCST-PE	13	7-23.75	5	4.75-10	U = 241 z = -3.1	0.002	0.4
WCST-NE	13	6.5-23.25	4.5	3-11.25	U = 254 z = -2.9	0.003	0.37
WCST-CL	64.5	58.75-73.25	64	61-67.25	U = 436.5 z = -.2	n.s.	0.02
WCST-CN	6	3-6	6	6-6	U = 304.5 z = -2.83	0.003	0.36
WCST-NT	16	11-24	12	11-16.25	U = 299.5 z = -2.24	0.024	0.28
WCST-LS	1	0-1.25	0	0-1	U = 308 z = -2.33	0.02	0.3

Note. OCD, obsessive-compulsive disorder; DSF, Digit Span Forward; DSB, Digit Span Backward; CBTT, Corsi Block Tapping Task; SER, Stroop Test Errors Reading Condition; SEC, Sroop Test Errors Colour Naming Condition; SEI, Stroop Test Errors Interference Condition; SRTR, Stroop Test Reaction Time Reading Condition; SRTC, Stroop Test

Reaction Time Colour Naming Condition; SRTI, Stroop Test Reaction Time Interference Condition; WCST, Wisconsin Card Sorting Test; WCST indices: TA, Trials administered; TE, total errors; PE, perseverative errors; NE, nonperseverative errors; CL, conceptual level response; CN, number of categories completed; NT, number of trials to complete first category; LS, failure to maintain set; n.s., not significant. WCST scores represent raw scores. Reaction time on the Stroop Task was measured in msec.

Table 3

The distribution of OCD patients in terms of average healthy adult group scores (data represent percent scores)

Task	Functions measured	1SD+	1SD-	2SD+	2SD-
DSF	short term verbal memory	36.66	50	6.66	3.33
DSB	short term verbal memory	60	40	0	0
CBTT	short term visuo-spatial memory	30	70	0	0
SEII	inhibition	53.33	13.33	0	33.33
WCST-PE	shifting	26.66	36.33	0	30

Note. OCD, obsessive-compulsive disorder; SD, standard deviation; 1 SD+/-, percent of patients are within 2 SD of the healthy adults mean; 2 SD+/-, percent of patients are above 2 SD of the healthy adults mean; DSF, Digit Span Forward; DSB, Digit Span Backward; CBTT, Corsi Block; SEII, Stroop Error Inhibition Index (Errors Interference Condition – Errors Colour Naming Condition); WCST-PE, Wisconsin Card Sorting Task perseverative errors.

DISCUSSION

Previous neuropsychological studies produced inconsistent results with tasks tapping short-term memory and executive functions in OCD. Our goal was to investigate the level of these cognitive functions in the same sample diagnosed with OCD. According to our results, OCD group performed within the healthy adults range in the short term memory tasks, while they produced severely impaired performance in executive tasks. Although, a significant group difference was found for Corsi Block Tapping Task, the percent distribution analysis revealed that none of the OCD patients performed in the seriously impaired range (above two standard deviations of the average healthy control group scores). Each OCD patients in our sample performed within the normal range (one standard deviation of the average control scores). Based on this, despite the average group difference in the Corsi scores there is no sign of impairment of spatial short term memory functions in our OCD sample.

The OCD patients were significantly slower in all three conditions of the Stroop Task, and there was a tendency toward significance at the level of committed errors in the interference condition. We suggest, that the inability to inhibit a prepotent response in the Stroop task is a consequence of the impairment of inhibitory executive functions in OCD.

Our study confirms earlier reports showed that OCD patients produced impaired performance in the WCST[25,26] in almost all aspects of the task: OCD patients committed significantly more total errors, perseverative errors and non-perseverative errors, completed fewer categories, required more trials to complete the first category, and showed more failures to maintain set compared to healthy control group.

The higher number of perseverative errors in WCST is a good index of a shifting deficit, which could also be the consequence of impaired inhibitory mechanisms, consistently linked to dorsolateral prefrontal deficit. [27,28]. We argue that set-shifting also requires the ability to inhibit previously acquired rules, a process mediated by the orbitofrontal cortex, an area

which might be impaired in OCD. [9] In sum, inhibitory failures caused by the abnormalities of orbitofrontal and dorsolateral prefrontal cortex are likely to play a crucial role in the appearance of perseverative errors in the WCST.

The presence of perseverative responses correlated with the severity of symptoms, patients with higher Y-BOCS scores committed more perseverative errors.

Our findings are also in line with results showing that patients in the recovered phase of the illness had significant impairments in set-shifting tasks, which is a possible candidate for endophenotypic marker for OCD. [52]

The significantly more errors in the failure to maintain set indices could be interpreted as an attention deficit impairment[53], which might be a consequence of the hyperactivity of the anterior cingular cortex in OCD. [20,54]

Based on the results of the short term memory tasks, we can conclude that updating component of the working memory system seems to be intact in OCD. [14] Short term memory scores of the OCD group were in the healthy range. Note, that Digit Span Backward Task, which requires a constant updating of the contents in short term memory, is a more difficult probe then the Digit Span Forward Task, and the performance of the patients is not impaired.

Our results support the view that executive functions are altered in OCD. The general executive function deficit could be explained by the failures of inhibition mechanism. These results support the neuropsychological model of OCD the deficit of cognitive and behavioral inhibition are responsible for the main cognitive findings of this disorder, most prevalently the deficit in set shifting and prepotent response inhibition. [9]

There were some limitations to our study. First we used a heterogeneous group of patients and did not use subgroups. Second, the majority of the patients were under medication during the study. Third, we based our conclusions on the few neuropsychological tasks selected for this study.

Further research is needed to clarify the exact nature of inhibitory executive processes and their contribution to the cognitive neuropsychological profile and symptoms of the disorder.

Acknowledgement

Financial support for the research was provided by OTKA (Hungarian National Science Foundation) K84019. Gyula Demeter was supported by the Pro Progressio Foundation scholarship.

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6.2. Study 2: Impaired PM functions in OCD

Racsmány, M., Demeter, Gy., Csigó, K., Harsányi, A. & Németh, A. (2011). An experimental study of prospective memory in obsessive-compulsive disorder. *Journal of Clinical and Experimental Neuropsychology, 33*, 85-91. DOI: 10.1080/13803395.2010.493147.

JOURNAL OF CLINICAL AND EXPERIMENTAL NEUROPSYCHOLOGY
2010, *iFirst*, 1–7

Psychology Press
Taylor & Francis Group

An experimental study of prospective memory in obsessive-compulsive disorder

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The aim of the present study was to investigate prospective memory (PM) function in patients with obsessive-compulsive disorder (OCD). An event-based PM task was administered to 30 OCD patients and 30 healthy adult participants. For OCD patients, PM instruction produced significantly more cost in terms of reaction time (RT) during the ongoing task. A significant group–experimental condition interaction in ongoing task RTs was found, which suggests that PM instruction loaded an extra cost onto OCD patients' ongoing activities, and this was independent of the execution of the PM intention. Comparing the PM task RTs between patients and healthy adults also revealed a significant group difference. These results suggest that OCD patients experience difficulties during PM tasks, and these difficulties originate from overmonitoring the stimuli for PM cues.

Keywords: Obsessive-compulsive disorder; Intention maintaining; Prospective memory; Monitoring functions.

INTRODUCTION

Obsessive-compulsive disorder (OCD) is a psychiatric condition that is defined by the presence of either obsessions (intrusive, disturbing thoughts) or compulsions (repetitive, unwanted behaviors). OCD has been associated with various cognitive deficits. The clinical presentation of this disorder has prompted researchers to investigate the integrity of executive functions and controlled memory processes based mainly on frontostriatal and frontotemporal neural circuits (van den Heuvel et al., 2005). Although the results of neuropsychological studies of OCD are inconsistent, there is evidence suggesting that OCD patients have difficulties with tasks involving strategy planning, attentional shifting, inhibition of prepotent responses, and self-cued memory retrieval processes (Abbruzzese, Bellodi, Ferri, & Scarone, 1995; Chamberlain, Blackwell, Fineberg, Robbins, & Sahakian, 2005; Christensen, Kim, Dysken, & Hoover, 1992; Gambini, Abbruzzese, & Scarone, 1993; Greisberg & McKay, 2003; Purcell, Maruff, Kyrios, & Pantelis, 1998; Rubin & Harris, 1999). It was recently suggested that prospective memory (PM) is also impaired in OCD patients, and this PM deficit is a major contributor to the cognitive phenotype of this disorder. By involving subclinical checkers, Cuttler and Graf (2007, 2009) produced compelling evidence that a checking compulsion is associated with a deficiency in event-based PM tasks. Marsh et al. (2009) found that people with obsessive-compulsive tendencies (washing compulsions) manifest deficits in an event-based PM task for neutral intentions. This performance was ameliorated by giving the subclinical group an intention about a threat-related category. PM refers to the encoding, storage, and delayed retrieval of intended actions (Einstein & McDaniel, 1996; Ellis, 1996).

Several neuroimaging studies have found that the maintenance and execution of PMs prompt activation in a distributed network. This network includes structures

Financial support for the research was provided by OTKA (Hungarian National Science Foundation) K68463 and IN77932. Mihály Racsmány is grantee of the Bolyai János Research Scholarship of the Hungarian Academy of Science. The authors thank Attila Keresztes and two anonym reviewers for their valuable comments.

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http://www.psypress.com/jcen DOI: 10.1080/13803395.2010.493147

within the rostral prefrontal cortex (PFC), parietal cortex, hippocampal complex, and right thalamus (Burgess, Quayle, & Frith, 2001; Burgess, Scott, & Frith, 2003; Okuda et al., 2007; Okuda et al., 1998; West, 2008). Without intact PM functions, one would be unable to carry out long-term plans and intentions (as is the case following sustained damage to various frontal areas). In addition, such an individual would be situated in a condition that can be described as lacking a cognitive future (Burgess, 2000; Kliegel, Jager, Altgassen, & Shum, 2008). On the contrary, overactivated intentions in a PM system would cause persistent thoughts and actions. Without the proper cancellation of these intentions, one's cognitive system would become overwhelmed by future thoughts and acts. Experimental research on PM has identified a number of components of prospective remembering, such as formation, retention, execution, and evaluation or monitoring of intentions (Kliegel, Martin, McDaniel, & Einstein, 2002). Although monitoring has a long history in the memory retrieval field, it has only recently become a topic of interest in the event-based PM research field (Guynn, 2003). Three widely known monitoring theories have been developed in the last two decades, and all of these models describe monitoring as a strategic process.

The supervisory attentional system (SAS) model states that actions are controlled on two levels (Burgess & Shallice, 1997; Norman & Shallice, 1986). The first level, contention scheduling, is automatic and controls routine behaviors when environmental cues are sufficient to trigger appropriate behavior. The second level is the SAS biasing contention scheduling and monitoring the environment for target events that indicate when it is appropriate to execute the intended prospective performance.

The multiprocess model proposes that although PM is supported by automatic processes when there is a strong association between the PM target event and the intended actions, there are other circumstances when PM performance is mediated by more strategic monitoring processes (McDaniel & Einstein, 2000; McDaniel, Guynn, Einstein, & Breneiser, 2004). There are situations when, for example, the PM target events are not salient, or there is no strong association between target events and the intended action. Finally, the preparatory attentional and memory processes model (PAM) proposes that nonautomatic attentional processes are always involved in PM retrieval (Smith, 2003; Smith & Bayen, 2004). One component of these preparatory attentional processes is monitoring for the PM target events that indicate the appropriate time for PM actions.

Although these influential models propose that monitoring is a strategic process, there is a recent concept that proposes that monitoring comprises two processes that demand resources: instantiating a PM retrieval mode and making periodic checks of the environment for an appropriate target to execute the intended action (Guynn, 2008). Based on these advances, PM research produced dependent measures that were developed to analyze the role of monitoring functions in PM responses. These measures are the accuracy and latency of the ongoing activities in which the PM task is embedded (Guynn, 2003; Kliegel, Martin, McDaniel, & Einstein, 2001, 2004). According to Guynn (2008), the principal way to measure monitoring in an event-based PM task is to compare the performance on an ongoing task, during which PM instructions or targets are embedded (experimental trials), with the performance on the same task when no PM instructions or cues are assigned (control trial). The lower accuracies or higher latencies on the experimental trials than on the control trials provide evidence of monitoring activity (Guynn, 2003; Kliegel et al., 2001, 2004; Marsh, Hicks, & Cook, 2005). In a seminal paper, Burgess et al. (2001) adapted these methodologies for a positron emission tomography study. Healthy participants were instructed to perform one of four tasks under three conditions: a baseline condition where only the ongoing activities were performed, a prospective expectation condition where prospective cues were expected but never occurred, and an execution condition where prospective cues were presented. The researchers found activation in the frontal pole (middle frontal gyrus), right parietal lobe, and precuneus region in both the expectation and the execution conditions relative to the baseline condition. This result was interpreted as evidence that the activated network supports the maintenance of intentions during the course of ongoing activity. The differences revealed by the comparison of the expectation and execution conditions—the activation of the right thalamus accompanied by decreases in the right dorsolateral prefrontal cortex (RDLPFC)—seemed to be associated with the realization of delayed intentions. An important conclusion of this study was that the activation of the rostral PFC reflects sustained processing related to checking for a prospective cue (West, 2008).

The aim of the present study was to investigate PM functions in OCD patients, both in an expectation and in an execution condition. We applied one of the tasks from the Burgess et al. (2001) study (Task 1) outlined above; this specific task was selected because of its relative ease, as indicated by the low rates of misses and false alarms in the original study. Furthermore, this task appeared suitable for an experimental study involving medicated patients. The specific design of the task allowed us to investigate the function of monitoring processes for PM cues in OCD patients. We hypothesized that PM instruction would cause an extra cost in ongoing activity for OCD patients, and this was expected to be independent of the execution of the delayed intention.

METHOD

Experimental design and procedure

We closely followed the protocol established by Burgess et al. (2001). An event-based PM task was administered to each participant under three conditions: (a) a baseline condition in which there was no expectation that PM stimuli would occur, and no PM stimuli occurred; (b) an expectation condition in which participants were told that PM stimuli might occur, though none actually did;

and (c) an execution condition in which participants were told that PM stimuli might occur, and stimuli did occur. This procedure allowed us to separate and compare the performances associated with intention maintenance and its realization.

A total of 60 stimuli were presented in the baseline and expectation conditions. The execution condition contained PM stimuli that were pseudorandomly distributed, amounting to 25% of the stimuli. In each condition, the first 6 stimuli were considered practice items and were not included in the analysis. The order of the conditions (baseline, expectation, and execution) was the same for all participants. Stimuli presentation strictly adhered to the Burgess et al. (2001) procedure and was participant paced (i.e., the onset of the next stimulus was cued by the participant's response, and the stimuli remained visible until that response occurred). A 2,000-ms blank-white-screen interval was inserted between presentations.

In each trial, two arrows were presented on the display (see Figure 1). One arrow was always black, and its position varied pseudorandomly. In both the baseline and the expectation conditions, stimuli included 30 items in which the black arrow pointed to the left and an additional 30 items in which it pointed to the right. The ratio in the execution condition was 40/40. Two color bars also appeared on the screen and were located at equal distances above and below the arrows. The color of the horizontal bar was red, blue, green, yellow, or orange.

Participants were positioned with the forefinger, middle finger, and third finger of their right hand on the three arrow keys of a computer keyboard. They were told to press the key with their forefinger if the black arrow was pointing to the left, with their third finger if it was pointing to the right, and with their middle finger if the two color bars above and below the arrows were the same color. Written instructions were read to the participants immediately before each experimental block was administered. Participants were asked to press the key with their forefinger if the arrow was to the left of a fixation point and with their third finger if it was to the right. They were told to respond with their middle finger if the two color bars above and below the fixation point were the same color on any trial.

Participants

A total of 30 properly diagnosed OCD patients were selected from the Nyírő Gyula Hospital, Department of Psychiatry I and II, Budapest, Hungary (mean age = 33.46 years, *SD* = 10.81; mean education = 12.86 years, *SD* = 2.59). Patients either were being followed for OCD treatment or had been followed in the past. Individuals were included in the study if they had a *DSM–IV* (*Diagnostic and Statistical Manual of Mental Disorders–Fourth Edition*; American Psychiatric Association, 1994) diagnosis of OCD and were between 18 and 65 years old. A psychiatrist (A.H.) confirmed the diagnosis following the Structural Clinical Interview for DSM–IV Axis I Disorders (SCID-I; First, Spitzer, Gibbon, & Williams, 1997). Severity of OCD symptomatology was assessed with the Yale Brown Obsessive-Compulsive Scale (mean = 26.36; *SD* = 7.37). We excluded participants from the study who met the criteria for depression (Revised Hamilton Depressive Rating Scale, mean = 10.5; *SD* = 6.34); we also excluded participants with any other current comorbid psychiatric diagnosis (Axis I or Axis II). Participants completed a questionnaire about their drug use, and those patients with a history of drug abuse in the last year were excluded.

All OCD patients received the following evaluations: a psychiatric interview by experienced clinicians (M.D.) and an assessment by trained raters that included the SCID-I (First, Spitzer, Gibbon, & Williams, 1995) to confirm current Axis I *DSM–IV* disorders, the Yale-Brown Obsessive Compulsive Scale (Y-BOCS; Goodman et al., 1989a; Goodman, Price, Rasmussen, & Mazure, 1989b), and the Hamilton Rating Scale for Depression (HAM-D, 17-item; Hamilton, 1960).

Written informed consent was obtained prior to the study (see Table 1 for patient characteristics). The project was approved by the institutional ethical review board. After being given a detailed description of the investigation by the clinicians, patients were asked to sign an informed consent document. All patients were assured that participation in the study would not interfere with their clinical treatment. The healthy adult group was matched according to age and education (mean age = 33.03 years, *SD* = 11.76; mean education = 13.5, *SD* = 2.71).

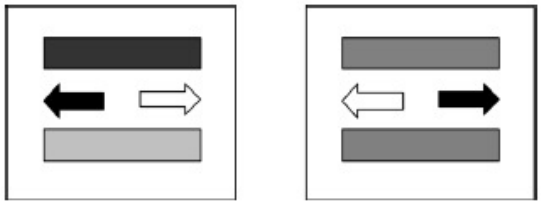

Figure 1. Description of the tasks: (a) Ongoing task: Press the key (left or right) in the direction of the black arrow. (b) PM task: If the color bars are the same color, press the up-arrow key.

RESULTS

As in the Burgess et al. (2001) study, errors for non-PM and PM stimuli were rare (see Table 2). The mean percentages of errors for the ongoing task were analyzed in a Group (patient, healthy adult) × Condition (baseline, expectation, execution) mixed analysis of variance (ANOVA). The same analysis was conducted on the mean percentages of the two types of errors (miss and false alarm) for the PM task. No significant differences were found.

Comparing patient and healthy adult group errors on the ongoing task baseline, $t(1, 58) = 0.85$, $p > .05$, $r = .11$, expectation, $t(1, 58) = 0.91$, $p > .05$, $r = .12$, and execution conditions, $t(1, 58) = 1.09$, $p > .05$, $r = .14$, revealed no significant differences.

We found the same results in the PM task execution condition with the miss type errors (not responding to a

TABLE 1
Sample demographics

	OCD (n = 30)			*Healthy adults (n = 30)*			*ANOVA*	
Characteristics	*N*	*M*	*SD*	*N*	*M*	*SD*	*F*	*p*
Age (years)		33.46	10.81		33.03	11.76	0.022	.882
Education (years)		12.86	2.59		13.50	2.71	0.853	.359
Sex (M/F)	20/10			21/9				
Y-BOCS Total		26.36	7.37					
HAM-D		10.5	6.34					

Note. OCD, obsessive-compulsive disorder; M, male; F, female; Y-BOCS, Yale-Brown Obsessive Compulsive Scale; HAM-D, Hamilton Rating Scale for Depression; ANOVA, analysis of variance.

TABLE 2
Hit rates in the three experimental conditions

		OCD (n = 30)		*Healthy adults (n = 30)*		*ANOVA*	
Hit rate (% correct)	*Task*	*%*	*SD*	*%*	*SD*	*F*	*p*
Baseline condition	Ongoing	98.83	4.87	99.61	0.97	0.735	.395
Expectation condition	Ongoing	98.83	3.69	99.66	0.67	1.479	.229
Execution condition	Ongoing	99.44	1.87	99.72	0.77	0.563	.456
	PM task	90.66	13.11	89.5	9.03	0.161	.690

Note. OCD, obsessive-compulsive disorder; PM task, prospective memory task, ANOVA, analysis of variance.

PM cue), $t(1, 58) = -0.18$, $p > .05$, $r = .02$, and the false-alarm type errors (responding to a PM cue when there should be no response), $t(1, 58) = -0.33$, $p > .05$, $r = .04$.

Analysis of RTs was based on errorless trials. The Group (patient, healthy adult) × Condition (baseline, expectation, execution) mixed ANOVA for the participants' mean reaction times (RTs) in the ongoing task showed a significant main effect of group, $F(1, 58) = 17.6$, $p < .01$, Cohen's $d = 1.1$, and condition, $F(1, 58) = 106.7$, $p < .01$, Cohen's $d = 2.71$. This analysis also produced a significant Group × Condition interaction, $F(2, 116) = 7.3$, $p < .01$ (see Figure 2).

Inspecting the data shown in Figure 2, it appeared to us that this interaction may be driven by an increase in RT of the execution condition in the healthy cohort. Therefore we carried out post hoc comparisons (Bonferroni) of participants' RTs in the expectation and execution conditions in both groups to check this assumption. Bonferroni corrected post hoc tests showed no significant difference in RTs of the ongoing task between the expectation condition and the execution condition in the OCD sample ($p > .1$). In contrast, the same comparison produced a significant difference within the healthy adult group ($p < .001$).

Comparison of patient and healthy adult group RTs on the ongoing task execution condition, $t(1, 58) = 3.96$, $p < .001$, $r = .46$, and on the PM task, $t(1, 58) = 3.9$, $p < .001$, $r = .46$, revealed significant differences (see Figure 3).

To further analyze the data, a "cost of PM instruction" was calculated for both the expectation (ongoing task RT in expectation condition – ongoing task RT in baseline condition) and execution (ongoing task RT in execution condition – ongoing task RT in baseline condition) conditions. Comparison of patient and healthy adult group expectation costs revealed a significant difference, $t(1, 58) = 3.59$, $p < .01$, $r = .43$, as did comparing the patient and healthy adult group execution costs, $t(1, 58) = 3.07$, $p < .01$, $r = .37$ (see Figure 4).

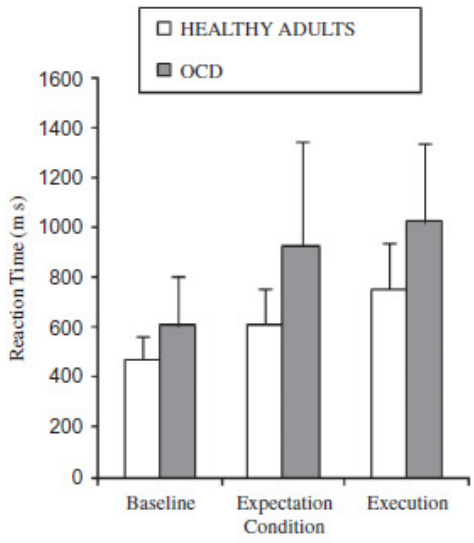

Figure 2. Mean reaction times (RTs) by condition for the ongoing task. Error bars show standard deviations. OCD = obsessive-compulsive disorder.

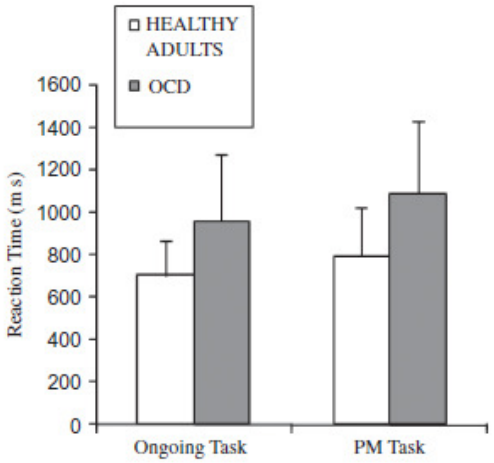

Figure 3. Mean reaction times (RTs) for the ongoing and PM tasks in the execution condition. Error bars show standard deviations. OCD = obsessive-compulsive disorder.

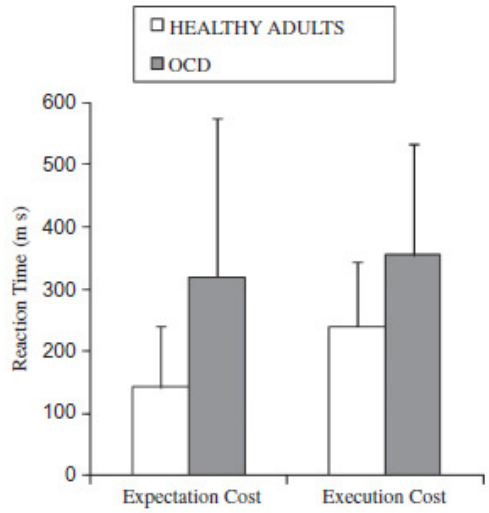

Figure 4. Mean reaction times (RTs) for the expectation and execution costs in the OCD and the healthy adult groups. Error bars show standard deviations. OCD = obsessive-compulsive disorder.

DISCUSSION

The present study involved the investigation of PM functions in OCD patients using an event-based PM experimental paradigm, and the study revealed some important differences between OCD patients and healthy adults. We found that OCD patients had longer reaction times during the ongoing task for all three conditions. While OCD patients had longer RTs than the healthy adult participants, the two groups performed similarly in terms of hits and misses. There was a significant group–experimental condition interaction for the ongoing task RTs, which suggests that PM instruction loaded an extra cost onto the ongoing activities of the OCD patients. This was independent of the execution of the PM intention, as there was no difference between the expectation and execution conditions. Patients were also significantly slower at the PM task, which indicates that their extra effort in searching for PM cues did not result in a better performance when PM cues appeared. Based on these results, we conclude that this interaction in the ongoing task RTs originated from OCD patients overmonitoring stimuli for PM cues following PM instruction.

CONCLUSION

The present study investigated PM function, a subcomponent of the executive system, in OCD patients using an event-based PM procedure. The performance of the OCD patients was impaired on the PM tasks, which suggests that this impairment originates from the overmonitoring of stimuli for PM cues. Previous findings are controversial concerning the relationship between OCD symptoms and prospective memory, as Cuttler and Graf (2007) found impaired PM functions in subclinical checkers, while Jelinek, Moritz, Heeren, and Naber (2006) found no PM impairment in OCD patients. The present paper is the first experimental study that showed differences in PM functions in OCD patients compared to healthy adults.

One way to explain these results is to assume that OCD patients produce a type of overactivation in monitoring for PM cues following PM instructions. This assumption would be consistent with some recent data suggesting that patients with OCD produce overactive performances in action-monitoring tasks (Johannes et al., 2001; Ursu, Stenger, Shear, Jones, & Carter, 2003). As Guynn (2008) pointed out, lower accuracies or higher latencies on the experimental trials than on the control trials provide evidence of monitoring activity (Guynn, 2003; Kliegel et al., 2001; Kliegel et al., 2004; Marsh et al., 2005). Based on these findings, it seems plausible that PM instruction prompted extra monitoring performance for PM cues in the OCD group, which interfered with the performance of the ongoing activities in both the expectation and the execution trials relative to the baseline.

Interpreting these results from a neuroscientific point of view, it is critical to investigate the results of Burgess et al. (2001) in detail, who applied the same procedure for healthy participants using positron emission tomography (PET). They found increased regional cerebral blood flow (rCBF) in the frontal pole (BA10) bilaterally and also in the right lateral prefrontal cortex, inferior parietal cortex, and precuneus in the expectation and execution conditions relative to the baseline condition These rCBF increases were accompanied by significant rCBF decreases in the insula of the left hemisphere. Importantly, they found decreased rCBF in left frontotemporo networks (insula gyrus, precentral gyrus) when participants expected PM stimuli relative to the baseline (minus execution; see Burgess et al., 2001). Finally, the direct comparison of the execution and expectation conditions (execution minus expectation) revealed the activation of the right thalamus accompanied by

decreases in the right dorsolateral prefrontal cortex (RDLPFC). In the present study we found that PM instruction in the expectation and execution conditions produced the same amount of increase in RTs of the ongoing activity in the OCD group. Based on this, a plausible assumption would be that the activation of thalamus and DLPFC in OCD patients is at the same level when they only expect a PM cue and when they execute a PM action. Although there is no way to say more on this issue without neuroimaging investigations, it is an interesting assumption that OCD patients may produce a thalamic hyperactivation and DLPFC hypoactivation relative to healthy adults in PM expectation conditions. Thalamus is implicated in anticipatory attentional processes and in the monitoring of self-generated actions (Blakemore, Rees, & Frith, 1998; Portas et al., 1995). Recent neuroimaging studies found increased glucose metabolism in the thalamus, orbitofrontal cortex (OFC), caudate, prefrontal cortex, and anterior cingulate in patients with OCD as compared with healthy participants (Baxter et al., 1988; Nordahl et al., 1989; Swedo et al., 1989). These findings speak to the assumption that frontothalamic circuits may be overactivated in OCD patients in prospective memory task situations. This overactivation will result in an intensive monitoring performance for prospective cues. The smaller the probability of prospective cues is, the more maladaptive this monitoring behavior will be by slowing down ongoing behavior.

Although this is a plausible interpretation of our data, there are some limitations in our study design. First, we only used an event-based task and not a time-based PM task, and a time-based PM task would have allowed us to directly measure monitoring activity in terms of checking behavior (see Mackinlay, Kliegel, & Mäntylä, 2009). Second, we only found group differences in RTs and not in hits and misses, so a possible explanation of our data is that the group differences are the consequence of general inattention and not PM dysfunction. For example, Jelinek et al. (2006) found no PM impairments in OCD patients using the Rivermead Behavioural Memory Test. However, the major dependent variable in this study is the correct responses of the individuals in these simple tasks. We think that the reaction time data are more informative/sensitive in this case than the errors, which were almost zero in our study as a consequence of the construction of our task. In our opinion the overactivity of the PM system results in an overmonitoring activity in OCD patients, and the consequence of this overmonitoring is a slower reaction time in the ongoing task and in the PM task than in healthy adults. We think that these results could outline a new aspect of the treatment of OCD, as well. Considering that prospective memory deficit could contribute to both treatment adherence and many everyday difficulties in this disorder, including a prospective memory training in cognitive–behavioral therapy protocols of OCD seems a reasonable suggestion. Further experimental and neuroimaging work is needed to confirm the outlined assumptions.

Original manuscript received 23 November 2009
Revised manuscript accepted 28 April 2010
First published online day month year

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6.3. Study 3: Over-monitoring secondary task cues – PM deficit in OCD

METHOD

Participants

Twenty-six patients diagnosed with OCD who satisfied the diagnostic criteria in the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) (American Psychiatric Association, 1994) were examined at the Nyírő Gyula Hospital, Psychiatry II, Budapest, Hungary. A psychiatrist confirmed the diagnosis following the Structural Clinical Interview for DSM-IV Axis I Disorders (SCID-I) (First, Spitzer, Gibbon, & Williams, 1997). The severity of OCD symptoms was assessed using the Yale Brown Obsessive-Compulsive Scale (Y-BOCS) (Goodman et al., 1989a; Goodman, Price, Rasmussen, & Mazure, 1989b), while the severity of depression by the Hamilton Rating Scale for Depression (HAM-D, 21-item) (Hamilton, 1960; Warren, 1994). We excluded subjects who met the criteria for severe depression, or for any other comorbid psychiatric diagnosis (Axis I or Axis II) and also who had histories of drug abuse or neurological disorder. Regarding medication, 7 subjects were medication free, 5 took sertraline, 4 venlafaxine, 4 citalopram, 3 fluvoxamine, 2 clomipramine and 1 amfebutamone during the study.

Written informed consent was obtained prior to the study. The project was approved by the institutional ethical review board. After being given a detailed description of the investigation by the clinicians, patients were asked to sign an informed consent document. All patients were assured that participation in the study would not interfere with their clinical treatment. The healthy control group was matched according to age and education (see Table 1).

Table 1

Sample demographics and basic assessment results

Characteristics	OCD (*n*=26)		Healthy Control (*n*=26)		Idpendent Samples Test	
	Mean	S.D.	Mean	S.D.	t	p
Age (years)	31.23	9.67	29.73	11.19	.51	n.s.
Education (years)	14.07	2.34	15.11	2.45	-1.55	n.s.
Sex (M/F)	16/10		10/16			
PRMQ Total	41.73	16.33	29.00	5.82	3.74	<.001
RM Subscale	19.69	7.09	13.76	2.77	3.96	<.001
PM Subscale	22.03	9.72	15.23	4.28	3.26	<.01
DSF	6.23	0.95	6.69	1.01	-1.69	n.s.
DSB	5.03	1.03	5.23	1.17	-.62	n.s.
Y-BOCS Total	24.16	7.03				
Y-BOCS ORS	11.60	4.55				
Y-BOCS CRS	11.56	4.81				
HAM-D	11.40	7.10				

Note. OCD, obsessive-compulsive disorder; M, male; F, female; Y-BOCS Total, Yale Brown Obsessive Compulsive Scale Total score, Y-BOCS ORS, Yale Brown Obsessive Compulsive Scale, Obsessions-Severity Score; Y-BOCS CRS, Yale Brown Obsessive Compulsive Scale, Compulsions Severity Score; HAM-D, Hamilton Depressive Rating Scale; PRMQ Total, Prospective Retrospective Memory Questionnaire Total Raw Score; RM, Retrospective Memory Subscale Raw Score, PM, Prospective Memory Subscale Raw score; DSF, Digit Span Forward; DSB, Digit Span Backward, n.s., not significant.

Experimental design and materials

A modified event-based PM task was administered to each participant under two conditions: (1) a baseline condition in which no PM stimuli occurred and there was no expectation that they would occur (2) an execution condition in which participants were told that PM stimuli might occur and they did. The participants' task was to respond as quickly as they could to the

first PM stimulus and not to respond to the upcoming one, and so on. In other words, they had to not respond to each second PM stimulus.

The ongoing task was identical in the two conditions. Participants saw two digits at the same time on the screen, and their task was to press the left or right arrow keys on the keyboard in the direction of the numerically bigger digits. Participants received the PM instruction only in the execution condition; this instructed the participants that whenever they encountered two identical digits (the PM stimuli), their task was to press the up arrow key. They were also instructed that they needed to press the up arrow key only for each second occurrence of the PM stimuli. Participants were positioned with the forefinger, middle finger and third finger of their right hand on the three arrow keys of a computer keyboard. They were told to press with their forefinger if the bigger number was on the left side of the screen, with their third finger if it was on the right side, and with their middle finger if the two numbers were identical.

Sixty stimuli were presented in the baseline condition and 80 stimuli in the execution condition. The PM stimuli from the execution condition were pseudorandomly distributed, amounting to 25 per cent of the stimuli. In each condition the first six stimuli were considered practice items and were not included in further analysis. The order of the conditions (baseline and execution) was the same for all participants. The stimuli presentation was 500 ms and a 2000 ms blank white screen interval was inserted between presentations. In each trial two numbers between 1 and 10 were presented on the display (see Figure 1).

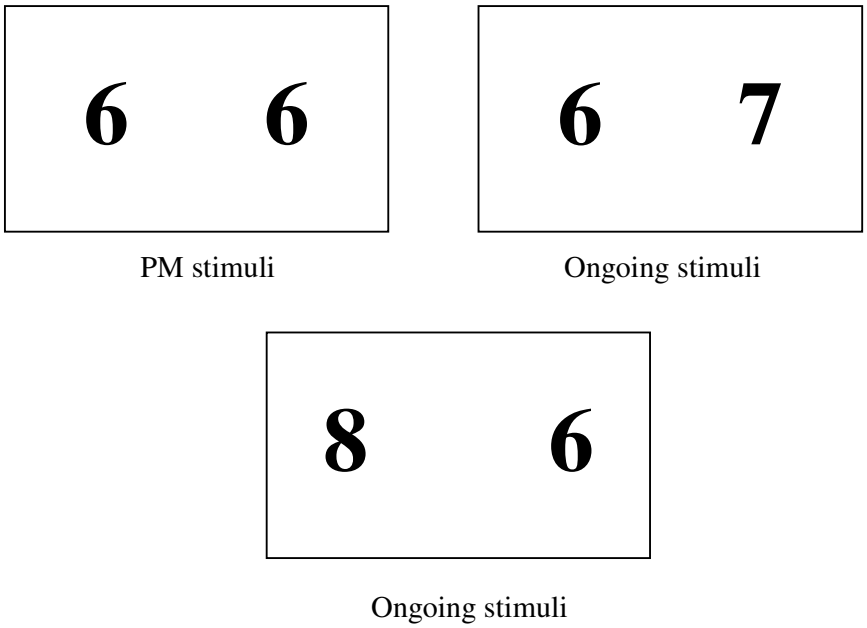

Figure 1. Examples for the PM and Ongoing Task stimuli in the execution condition

Written instructions were read to the participants immediately before each experimental block was administered. The experiment was run on the E-Prime experimental software.

Yale-Brown Obsessive-compulsive Scale (Y-BOCS)

The obsessive-compulsive symptomatology was assessed with the Y-BOCS (Goodman et al., 1989a; Goodman et al., 1989b). The Y-BOCS is a clinical semistructured interview that assesses the severity of obsessional and compulsional symptoms (see a detailed description in Hungarian by Demeter, 2010b). The severity of obsessions and compulsions are rated using a five point Likert scale ranging from 0 to 4, with higher scores indicating greater severity. The 10 severity items which asses frequency, interference, distress, resistance and symptom control, yield three scores: an Obsessions-Severity Score (range = 0-20), a Compulsions Severity Score (range = 0-20) and a Total Score (range =0-40). Mild cases score 10-20 points, moderate cases score 21-30 points and severe cases score 31-40 points.

Hamilton Depression Rating Scale (HAM-D)

The HAM-D is a 21 item multiple choice clinician-administered questionnaire that measures the severity of depressive symptoms in individuals (Hamilton, 1960; Warren, 1994). The most widely accepted cut-off scores are: <8, normal; 8-13, mild depression; 14-18, moderate depression; 19-22, severe depression, >23, very severe depression (Endicott, Cohen, Nee, Fleiss, & Sarantakos, 1981; Kearns et al., 1982.)

Prospective and Retrospective Memory Questionnaire (PRMQ)

PRMQ is a standardized self-report measure of prospective and retrospective memory failures in everyday life (Smith, Della Salla, Logie, & Maylor, 2000). Contains 16 simple questions, 8 questions are about prospective and 8 about retrospective memory, grouped in two subscales respectively.

Subject for each item indicate on a Lickert type 5 point scale the frequency of facing certain type of memory failures (1 = never; 2 = a little; 3 = quite a lot; 4 = a lot; and 5 = very often). Higher scores indicate a greater frequency of memory failures. The items were also designed

to contain an equal number of items concerned with either self-cued memory or environmentally-cued memory, and with short-term versus long-term memory.

Digit Span Forward (DSF) and Digit Span Backward Task (DSB)

We used the DSF and DSB Tasks as measures of verbal short-term and working memory. In both tasks trials consisting of a series of increasing numbers are presented orally by the examiner at a rate of one digit per second. The numbers needed to be repeated by the subject in the same (forward span) or in the reverse order (backward span). In our version each trial consisted of four series of equal length, and we considered a trial as completed if the subject reproduced at least two correct series. The number of correctly recalled trials for forward and backward span was counted (see Table 1).

Procedure

All patients received the following evaluations: a psychiatric interview by an experienced clinician (M.D.); an assessment by trained raters that included the Structured Clinical Interview for DSM-IV to confirm current Axis I DSM-IV disorders (First et al., 1997), the Y-BOCS (Goodman et al., 1989a; Goodman et al., 1989b) and the HAM-D, 21-item (Hamilton 1960; Warren, 1994). The patients completed the PRMQ (Smith et al., 2000), and a trained neuropsychologist assed the verbal short-term memory and run the event based PM experiment. The evaluations took part in separate sessions.

RESULTS

Statistical analyses were performed using mixed analysis of variance (ANOVAs) with an alpha level set at .05, two-tailed t-tests and bivariate correlation (Pearson correlation coefficient). Eta squared (η^2) was used as a measure of the effect size for ANOVA and r for the t-test analyses (Cohen, 1988; Field, 2005).

We analyzed separately errors and reaction times (RTs). The mean percentages of errors for the ongoing task were analyzed in a Group (patient, healthy adult) X Condition (baseline, execution) mixed analysis of variance (ANOVA) (see Table 2).

Table 2

Hit rate in the two experimental condition

Hit rate (% correct)	OCD (*n*=26)		Healthy Control (*n*=26)		Idependent Samples Test	
	%	S.D.	%	S.D.	t	p
Baseline condition – Ongoing Task	98.07	3.93	98.07	1.86	0.00	n.s.
Execution condition – Ongoing Task	96.93	5.35	98.77	1.38	-1.7	n.s.
Execution condition – PM Task	89.42	10.13	95,76	6.43	-2.69	<.05

Note. OCD, obsessive-compulsive disorder; PM task, prospective memory task; n.s., not significant.

We found a significant Group X Condition interaction, $F(1, 50) = 5.04$, $p < .05$, $\eta^2 = .09$. The same analysis was conducted on the mean percentages of the two types of errors (misses and false alarms) for the PM task. There was significant effect of group, $F(1, 50) = 7.47$, $p < .01$, $\eta^2 = .13$. Comparing patient and healthy adult group errors on the ongoing task in the baseline condition, $t(1, 50) = 0$, $r = 0$, and in the execution condition, $t(1, 28) = 1.70$, $r = .30$ revealed no significant differences. In the execution condition we found no significant difference $t(1, 42) = 1.51$, $r = .23$ for miss type errors (not responding to a PM cue), but it was found a significant difference for the false alarm type errors (responding to a PM cue when there should be no response), $t(1, 35) = 2.27$, $p < .05$, $r = .36$ (see Figure 2).

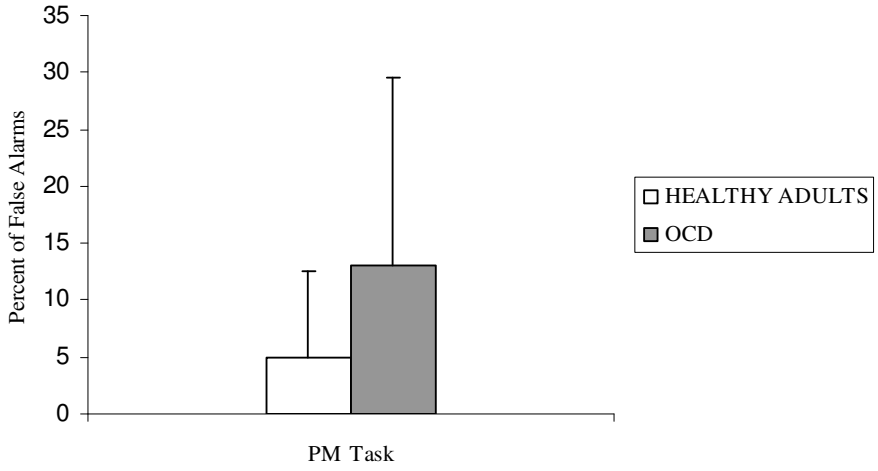

Figure 2. Percent of false alarm type errors on the PM task

Note. Error bars show standard deviations. PM Task = prospective memory task, OCD = obsessive compulsive disorder.

Analysis of RTs was based on errorless trials. The Group (patient, healthy adult) × Condition (baseline, execution) mixed ANOVA for the participants' mean RTs in the ongoing task showed a significant main effect of group, $F(1, 50) = 4.95$, $p < .05$, $\eta^2 = .09$, and condition, $F(1, 50) = 88.75$, $p < .001$, $\eta^2 = .64$. This analysis also produced a significant Group × Condition interaction, $F(1,50) = 4.00$, $p = .05$, $\eta^2 = .03$ (see Figure 3).

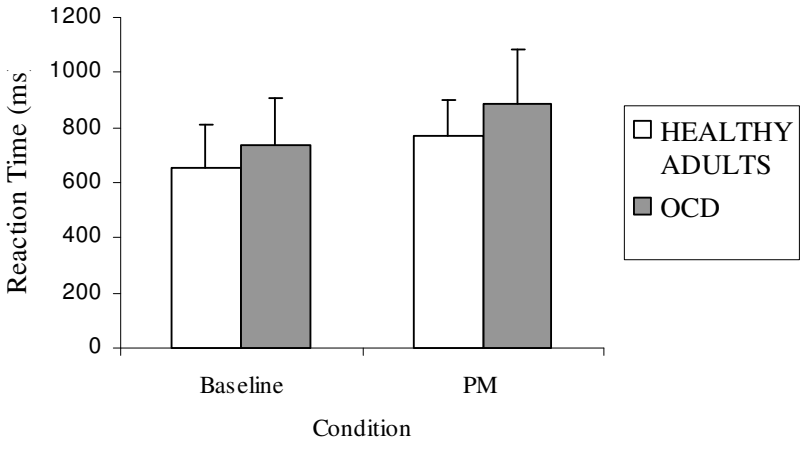

Figure 3. Mean reaction times (RTs) by condition

Note. Error bars show standard deviations. PM = execution condition, OCD = obsessive compulsive disorder.

Comparison of patient and healthy adult group in the execution condition revealed significant difference of RTs for the ongoing task $t(1, 43) = 2.59$, $p < .05$, r = .37, but there was no significant difference for the PM task, $t(1, 50) = 1.45$, $r = .20$ (see Figure 4).

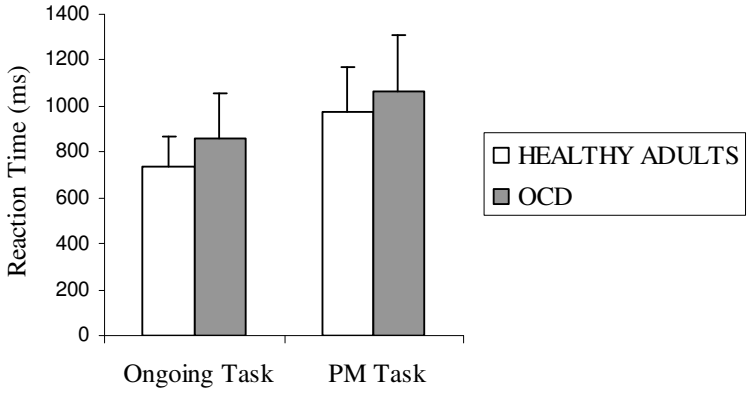

Figure 4. Mean reaction times (RTs) for the ongoing and PM tasks in the execution condition

Note. Error bars show standard deviations. PM Task = prospective memory task, OCD = obsessive compulsive disorder.

To further analyze the data, a "cost of PM instruction" was calculated for execution condition (ongoing task RT in execution condition – ongoing task RT in baseline condition). Comparison of patient and healthy adult group execution cost revealed a significant difference, $t(1, 50) = 2$, $p = .05$, $r = .27$ (see Figure 5).

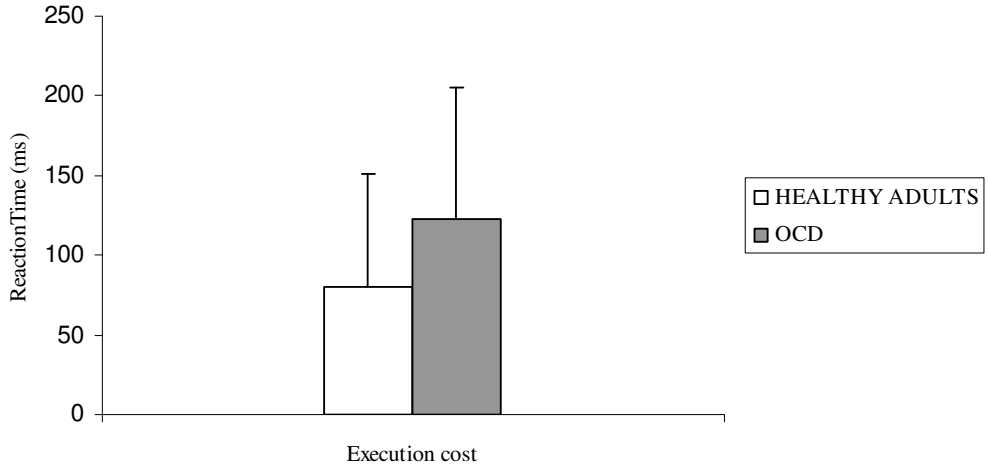

Figure 5. Mean reaction times (RTs) for the execution costs in the two groups

Note. Error bars show standard deviations. OCD = obsessive compulsive disorder.

Idependent T-test showed a significant group difference on the PRMQ Total scores $t(1, 50) = 3.74$, $p < .001$, $r = .47$, on the PRMQ PM subscale $t(1,50) = 3.26$, $p < .01$, $r = .42$, and on the PRMQ RM subscale $t(1, 50) = 3.96$, $p < .001$, r = .49. However, there was no significant group difference in the Digit Span Forward $t(1, 50) = -1.69$, r = .23 and in the Digit Span Backward tests $t(1, 50) = -.62$, r = .09 (see Table 1). A significant positive correlation was found between the number of false alarm type errors in the PM task and the scores obtained in the PM subscale of the PRMQ by the OCD group ($r = .43$, $p < .05$).

CONCLUSION

The aim of the present study was to investigate prospective monitoring and response inhibition functions in OCD with a modified event-based PM task. It was found that OCD patients made significantly more false alarm errors and had longer reaction times in the prospective execution condition than healthy control subjects. This result may reflect the fact that OCD patients had difficulties in inhibiting their PM response whenever they encountered a PM cue. Moreover, there was a significant group experimental condition interaction for the ongoing task RTs. This later difference can be interpreted as PM instruction loading an extra cost on the ongoing activities in the case of OCD patients. These results are in line with our previous findings. In the present study we did not find a significant improvement in the PM task compared to healthy adults, which can mean that extra monitoring activity did not result in better PM performance. One possible explanation is that OCD patients in the execution condition have forgotten that they responded to a target before, as a consequence of their short-term memory problem. However, this explanation does not seem to be a valid one as there was no sign of a working memory problem of the present OCD group, as they produced a similar performance on the DSF and DSB probes to the matched healthy control group. Patients achieved significantly higher scores on the PRMQ – which is a subjective evaluation of the prospective and retrospective performance – and this may mean that in their everyday life they regularly experience memory problems. It seems to be an important result that patients with higher scores on the PM subscale of PRMQ made significantly more errors (false alarms) on the PM task. There was no significant correlation between Y-BOCS total scores and number of errors or mean reaction times obtained for the entire task, which means that the severity of the disorder did not affect the level and the speed of general performance on this task. Based on the hit rates on the PM task and the reaction time scores on the ongoing

task in the execution condition, it can be concluded that OCD patients' performance can be explained by over-monitoring for PM cues.

6.4. Study 4: Long-term effects of retrieval practice

Racsmány, M., Conway, M.A. & Demeter, Gy. (2010). Consolidation of Episodic Memories During Sleep: Long-Term Effects of Retrieval Practice. *Psychological Science, 21,* 80-85. DOI: 10.1177/0956797609354074.

Research Article

aps ASSOCIATION FOR PSYCHOLOGICAL SCIENCE

Consolidation of Episodic Memories During Sleep: Long-Term Effects of Retrieval Practice

Psychological Science
21(1) 80–85

DOI: 10.1177/0956797609354074
http://pss.sagepub.com
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Abstract

Two experiments investigated the long-term effects of retrieval practice. In the retrieval-practice procedure, selected items from a previously studied list are repeatedly recalled. The typical retrieval-practice effects are considerably enhanced memory for practiced items accompanied by low levels of recall, relative to baseline, for previously studied items that are associated with the practiced items but were not themselves practiced. The two experiments demonstrated that the former effect persisted over 12 hr; the latter effect also persisted over 12 hr, but only if a period of nocturnal sleep occurred during the retention interval. We propose that consolidation processes occurring during sleep, and possibly featuring some form of off-line rehearsal, mediate these long-term effects of retrieval practice.

Keywords

retrieval practice, episodic memory, sleep, consolidation, rehearsal

Received 1/20/09; Revision accepted 4/29/09

It has long been thought that sleep plays a crucial role in the consolidation of recently formed memories. Current evidence shows that retention of procedural knowledge can be enhanced by a period of sleep (Stickgold & Walker, 2005), as can retention of motor skills (Walker, Brakefield, Morgan, Hobson, & Stickgold, 2002). In a recent programmatic series of studies, Gaskell, Dumay, and their coworkers demonstrated that sleep is critical to the retention of new vocabulary, and in particular to the integration of newly acquired words into the lexicon (see Dumay & Gaskell, 2007, for a review). Furthermore, it has been observed that relatively few episodic memories formed during a day are retained the following day, which suggests that only a minority of episodic memories are selected for enduring retention (Conway, 2009; Williams, Conway, & Baddeley, 2008). According to one view, consolidation processes operating during sleep mediate these effects. Reactivation of the medial temporal lobe memory system, and especially hippocampal circuits, may be the locus of sleep-mediated consolidation (Wilson & McNaughton, 1994). Other brain areas have been implicated too, and it seems that networks in medial prefrontal cortex, operating at faster processing rates during sleep than during awake periods, rapidly and repeatedly replay processing sequences featured in the immediately preceding awake period (Euston, Tatsuno, & McNaughton, 2007). This mechanism may consist of a sequence of speeded off-line rehearsal, and possibly it is these intense bursts of rehearsal that lead to the consolidation of recent experience in long-term memory.

Consolidation processes operating during a nocturnal sleep cycle should influence the retention of recently formed episodic memories, and we explored this idea in two experiments using the retrieval-practice procedure (Anderson, Bjork, & Bjork, 1994; Racsmány & Conway, 2006). In this procedure, participants first study a list of words and then selectively practice recalling a subset of the list. Memory is then tested, typically by cued recall. The retrieval-practice procedure is particularly suited to exploring the consolidation of episodic memories, as it is thought that the study phase gives rise to the formation of an episodic memory of learning the study list and that the later practice phase gives rise to a pattern of activation and inhibition over the contents of the episodic memory. It is this pattern of activation and inhibition that mediates later access to memory content and that gives rise to the characteristic pattern of recall seen on the memory test (Racsmány & Conway, 2006). By this view, retrieval practice should give rise to long-term patterns of activation and inhibition that are strengthened by consolidation during sleep. The sole previous

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study of long-term retrieval-practice effects indicates that this may indeed be the case (MacLeod & Macrae, 2001), although we acknowledge that other researchers consider the effects of retrieval practice to be more likely short-term than long-term (Saunders & MacLeod, 2002; but see Anderson, 2001), and at least one current model (Norman, Newman, & Detre, 2007) proposes that REM sleep may "reset" inhibitory patterns. The retrieval-practice procedure was well suited for our study because it easily allows a period of sleep or equivalent period of wakefulness to be interposed between practice and test.

Experiment 1

In the retrieval-practice procedure, exemplars from various categories are first studied. After the study phase, selected items from selected categories are then repeatedly recalled, typically three times, in response to cues consisting of a category name plus word fragment. For example, if "fruit-orange" is a studied item, "fruit-o_____?" might be a retrieval-practice cue. The three phases of study, practice, and test usually are separated only by the few minutes required to give the instructions for each phase. The design yields three types of items: items that have been practiced (Rp+), items that have not themselves been practiced but that originate from a category for which another item has been practiced (Rp–), and items from categories for which no items have been practiced (Nrp).

The typical finding is that memory for Rp+ items is highest, memory for Nrp items is at an intermediate level, and memory for Rp– items is poorest. This pattern is taken to indicate strong activation of Rp+ items resulting from retrieval practice making these items highly accessible to recall, weaker activation of Nrp items, and inhibition of Rp– items (Anderson & Spellman, 1995; Bjork, Bjork, & Anderson, 1998; Racsmány & Conway, 2006; Storm, Bjork, Bjork, & Nestojko, 2006). According to this explanation, practice recalling an item from a previously studied set of category exemplars induces inhibition of exemplars that are not practiced and that could potentially compete with and disrupt recall of the cued items (cf. Anderson & Levy, 2007). Thus, studying "apple," "pear," and "orange" and then repeatedly practicing recall of only "orange" induces inhibition of "apple" and "pear." The net result is that memory for "apple" and "pear" (Rp– items) is hurt, whereas memory for "orange" (an Rp+ item) is enhanced. Other interpretations of these effects of retrieval practice have emphasized the role of interference rather than inhibition (e.g., Camp, Pecher, & Schmidt, 2007; see also Mensink & Raaijmakers, 1988).

In our first experiment, participants were assigned to two groups: a sleep group and a no-sleep group. The sleep group studied and practiced the items in the evening; the following morning, some 12 hr later and after their usual period of nocturnal sleep, their memory for the items was tested. The no-sleep group studied and practiced the items in the morning; 12 hr later, in the evening, their memory was tested.[1] We expected that the no-sleep group would not show the typical retrieval-practice effect and instead would simply show forgetting of the items. In contrast, and assuming that consolidation can enhance retention, we expected the sleep group to show the usual retrieval-practice pattern.

Method

Participants. Sixty-four undergraduate Hungarian students from the Budapest University of Technology and Economics (32 females, 32 males) participated in return for partial credit in an introductory psychology course. Their ages ranged from 19 to 26 years. There were 32 participants each in the sleep and no-sleep groups (16 females and 16 males randomly assigned within gender to each group). Note that all participants in the sleep group were tested a minimum of 1 hr after awakening.

Materials. Following Anderson et al. (1994), we used 10 categories, 2 of which were fillers. Each target and filler category consisted of 6 exemplars. Exemplars were moderate- to high-frequency words drawn from two Hungarian word-frequency norms (Füredi & Kelemen, 1989; Kónya & Pintér, 1985). For each subject, 4 target categories were practiced and 4 were nonpracticed; across subjects, each target category was equally often practiced and nonpracticed. The practiced and nonpracticed exemplars from practiced categories were counterbalanced over participants. In sum, in each learning session, participants learned 60 exemplars from 10 categories (2 of which were fillers), practiced 18 exemplars (including 6 fillers) from 6 categories (including the 2 filler categories), and finally tried to recall 60 exemplars (including 12 fillers) from the original 10 categories. During both practice and final cued recall, items from filler categories were always in the first and last positions in order to avoid the confounding effect of category position.

Procedure. Participants were randomly assigned to either the sleep or the no-sleep group. All participants completed a short questionnaire about the length and quality of their sleep period prior to the experiment. Those who had slept less than 4 hr or used sleeping pills were excluded from the experiment. The no-sleep group completed the sleep questionnaire only on the day of the experiment, answering the questions with reference to the previous night's sleep, whereas the sleep group completed the same sleep questionnaire on the day of the study phase and also on the day of the recall test, in each case answering the questions with reference to the previous night's sleep.

At 8 p.m., the sleep group completed the study phase followed by the practice phase; these participants returned to the laboratory for the surprise delayed recall test at 8 a.m. the following morning. Note that in all cases the test was given a minimum of 1 hr after awakening. The no-sleep group completed the study phase and practice phase at 8 a.m. and the surprise recall test at 8 p.m. on the same day. Neither group knew that they were returning to take a memory test; rather, all

participants were led to believe that they were returning to take part in a new and unrelated experiment.

In the study phase, participants were instructed that category-exemplar pairs would be presented on a computer screen and that they should study the pairs in preparation for a later memory test. Each category-exemplar pair was presented in uppercase letters in the center of the screen for 5 s. Order of presentation was semirandomized; exemplars from the same category did not appear on consecutive trials. When participants had completed the study phase, the experimenter distributed retrieval-practice booklets. Participants believed that this second phase was the memory test. Each page in the booklet showed one of the category names studied previously and the first two letters of one member of that category, also studied previously. Participants were instructed to complete the exemplar fragment with one of the words they had studied earlier. They were informed that some of the exemplars might be tested more than once and that in those cases they should respond with the remembered item. Rp+ items were repeated three times. At the end of the retrieval-practice phase, the booklets were collected, and participants were sent home for 12 hr. When they returned to the laboratory, they were given cued-recall booklets, in which the name of one of the previously studied categories appeared at the top of each page. Participants were instructed to recall as many examples as they could for each category in the 10-min period allocated for this test. They were instructed to complete the pages in order and not to return to a previous category once they had turned the page in the recall booklet. Order of presentation of the target categories was counterbalanced across participants.

Results

Planned comparisons revealed that the critical contrast of Nrp with Rp– items was reliable only in the sleep group, $t(1, 31) = -3.7$, $p_{rep} = .99$, $r = .55$ (for the no-sleep group, $t < 1$). Thus, the retrieval-practice effect was observed only in the sleep group (see Fig. 1 for mean percentages).[2] An independent t test revealed that there was no reliable difference between the two groups' recall of Rp+ items $t(62) = -1.12$; the long-term beneficial effect of selective practice (relative to baseline—i.e., Nrp items) was similar in the two groups. Debriefing interviews uncovered no evidence of conscious, intentional rehearsal in either group, and participants indicated that they were generally surprised by the delayed cued-recall test.

Experiment 2

A problem with the retrieval-practice procedure is that although it may induce inhibition of Rp– items, performance on Rp– items must almost certainly also be impaired by output interference from Rp+ items. Given that we were primarily interested in the effects of sleep on memory performance in the retrieval-practice procedure, this was in some respects a secondary issue. Nevertheless, in order to reduce the potential

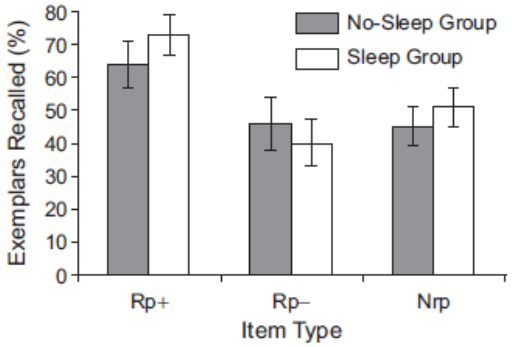

Fig. 1. Mean percentages of exemplars recalled by the sleep and no-sleep groups in Experiment 1. Results are shown separately for practiced items (Rp+), unpracticed items from practiced categories (Rp–), and unpracticed items from unpracticed categories (Nrp). Error bars show 95% confidence intervals.

effects of output interference, and also to further examine the effects of sleep on retrieval practice, we decided to run a replication of Experiment 1 in which output was more directly controlled. To achieve such control, we constructed a new study set in which the first letter of each word was unique within its category. At test, participants were cued with the category names and the first letters of studied items. Using these cues, we were able to control the order in which items were recalled. In addition, to control for potential time-of-day effects, we included a new control group who studied and practiced items at 8 a.m. and were then given the surprise recall test 1 hr later; we refer to this group as the morning no-sleep group. We reasoned that if the morning no-sleep group showed the retrieval-practice effect, then this effect might be attributable to the time of day of the test, rather than a period of sleep intervening between study and test.

Method

Participants. A new cohort of 96 undergraduate Hungarian students from the Budapest University of Technology and Economics (48 females, 48 males) participated in return for partial credit in an introductory psychology course. Their ages ranged from 20 to 28 years. There were 32 subjects in each of the three groups (16 females and 16 males randomly assigned within gender to each group). All participants in the sleep group and in the morning no-sleep group were tested a minimum of 1 hr after awakening.

Materials. Following Anderson et al. (1994), we used 10 categories, 2 of which were fillers. Each target and filler category consisted of 6 exemplars (as in Experiment 1). The exemplars were moderate- to high-frequency words drawn from two Hungarian word-frequency norms (Füredi & Kelemen, 1989; Kónya & Pintér, 1985). For each subject, 4 target categories were practiced and 4 were nonpracticed; across subjects, each

target category was equally often practiced and nonpracticed. The practiced and nonpracticed exemplars from practiced categories were counterbalanced over participants. The study list contained 6 words from each of the 10 categories, for a total of 60 words. Within each category, every word had a unique initial letter, so that a category name and first letter could serve as a specific cue for each target word.

Procedure. The procedure was the same as in Experiment 1 with the exception of changes in the cued-recall test. In that test, the cues appeared on a computer screen one at a time for 5 s each. Each cue consisted of a category name together with the first letter of one of the studied exemplars (e.g., "Fruit – O_____"). Items for each category were presented as a block; the cues for the three Rp– words were always presented first, in random order, and the cues for the Nrp and Rp+ items were then presented ungrouped and in random order. Participants wrote their responses in a response booklet.

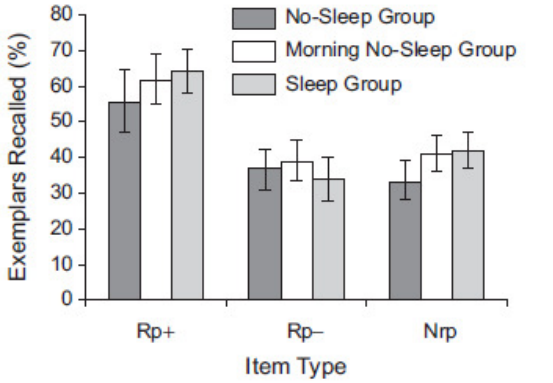

Fig. 2. Mean percentages of exemplars recalled by the sleep, no-sleep, and morning no-sleep groups in Experiment 2. Results are shown separately for practiced items (Rp+), unpracticed items from practiced categories (Rp–), and unpracticed items from unpracticed categories (Nrp). Error bars show 95% confidence intervals.

Results

Planned comparisons found that the critical contrast of Nrp with Rp– items was reliable in the sleep group, $t(1, 28) = -2.43$, $p_{rep} = .95$, $r = .43$, but not in the no-sleep group and the morning no-sleep group, ts < 1.2. Thus, the retrieval-practice effect was observed only in the sleep group (see Fig. 2). A one-way independent analysis of variance found no reliable difference between groups on recall of Rp+ items, $F < 1.2$, showing that the long-term beneficial effect of selective practice was present to the same degree in all groups (see Fig. 2). The debriefing interviews again indicated that participants did not rehearse items in the retention interval, and that all participants were surprised by the memory test. In sum, the overall pattern of findings replicated the pattern observed in Experiment 1 and indicates that output interference and time-of-day differences had little, or possibly no, influence in the two experiments.

Discussion

One account of the effects of retrieval practice posits that they are mediated by an episodic memory of the study phase (Racsmány & Conway, 2006). According to this view, which we term the *episodic-inhibition hypothesis* to distinguish it from accounts focusing on other types and sources of inhibition in long-term memory, retrieval practice establishes a pattern of activation and inhibition over the contents or features of an episodic memory of the study phase. As the episodic memory is consolidated in long-term memory, the pattern of activation and inhibition, which determines the accessibility of the contents of the memory, stabilizes and becomes resistant to further change. One major mechanism of this process of consolidation is rehearsal. According to the episodic-inhibition hypothesis, as a memory is repeatedly retrieved and its contents are accessed, its durability in long-term memory increases, and the accessibility levels of its contents become fixed (Racsmány & Conway, 2006; Racsmány, Conway, Garab, & Nagymáté, 2008).

The present findings suggest that sleep is important to this process of consolidation, as indeed other researchers using different procedures have also observed (e.g., Drosopoulos, Wagner, & Born, 2005). The findings of Experiment 2 indicate that retrieval-practice effects begin to dissipate after a retention interval of just 1 hr in the absence of rehearsal. Interestingly, in a related experiment not reported here, we found that if there is rehearsal in the retention interval, then retrieval-practice effects can be maintained over at least 12 hr (with no period of sleep). We use the term *rehearsal* here in a slightly nonstandard way, as according to our episodic-inhibition view, rehearsal occurs when a memory is activated and the pattern of activation and inhibition over its contents is instantiated. Such rehearsal does not have to occur consciously or intentionally, although, of course, it might. We suggest that when rehearsal occurs in this way, it approximates what has been termed *elaborative rehearsal* (Craik & Lockhart, 1972), and it promotes the integration of the memory with other memories and knowledge structures in autobiographical memory (see Conway, 2009). It is perhaps the degree and nature of the integration that determines the durability of access to a memory and its contents. Clearly, other memories formed during the retention interval may reduce integration, prevent it, or interfere with it in some other way. It seems likely that the opportunity for interference by new memories was greater in our no-sleep than in our sleep groups, and, consequently, integration may have been attenuated in the no-sleep relative to the sleep groups. (Note that this would not have been the case if rehearsal had been intentionally undertaken during the retention interval.)

According to this reasoning, the greater degree of integration of memories in the sleep groups underlies the long-term retrieval-practice effects we observed in these groups. This integration is, perhaps, similar in kind to the integration of new words with the lexicon found to occur after periods of nocturnal sleep (Dumay & Gaskell, 2007).

These novel long-term, sleep-related, retrieval-practice effects lend some support to suggestions that spontaneously occurring retrieval practice in everyday cognition may mediate aspects of remembering and forgetting (e.g., Anderson, 2001). But we can now add to this idea the notion that consolidation and integration processes occurring during sleep are also important in maintaining access to memories and their contents. The present findings demonstrate that consolidation of recently formed episodic memories during sleep may be integral to the normal functioning of episodic memory.

Declaration of Conflicting Interests

The authors declared that they had no conflicts of interests with respect to their authorship and/or the publication of this article.

Funding

Financial support for this research was provided by OTKA (Hungarian National Science Foundation) Grants K68463 and IN77932. Martin A. Conway is supported by a Professorial Fellowship (RES-051-27-0127) from the Economic and Social Research Council of Great Britain. Mihály Racsmány is grantee of the Bolyai János Research Scholarship of the Hungarian Academy of Science.

Notes

1. A very important design feature is that the memory test is unexpected. In a separate experiment not reported here, we found that long-term retrieval-practice effects can occur if participants rehearse the retrieval-practice items during the retention interval.

2. An alternative interpretation might focus on diurnal effects, such as the awakening cortisol response (ACR), which is thought to influence memory. However, as the ACR peaks and then begins to decline within 30 to 45 min following sleep (Clow, Thorn, Evans, & Hucklebridge, 2004), and all participants were tested at least 1 hr after awakening (and most were tested 90 to 120 min postsleep), it seems unlikely that the ACR could have directly influenced memory performance in the sleep group. Moreover, although cortisol levels begin to fall toward the onset of sleep and are at their lowest levels in the first 3 to 4 hr of sleep, all participants in the no-sleep group were tested several hours prior to sleep, and there is no reason to suppose that their cortisol levels had changed systematically at this point in the sleep/wake cycle. Thus, the sleep and no-sleep groups most likely had highly similar diurnal cortisol levels.

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6.5. Study 5: No retrieval induced forgetting (RIF) in OCD

METHOD

Participants

Nineteen patients diagnosed with OCD who satisfied the diagnostic criteria in the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) (American Psychiatric Association, 1994) were examined at the Nyírő Gyula Hospital, Psychiatry II, Budapest, Hungary. A psychiatrist confirmed the diagnosis following the Structural Clinical Interview for DSM-IV Axis I Disorders (SCID-I) (First, Spitzer, Gibbon, & Williams, 1997). The severity of OCD symptoms was assessed using the Yale Brown Obsessive-Compulsive Scale (Y-BOCS) (Goodman et al., 1989a; Goodman, Price, Rasmussen, & Mazure, 1989b; see a detailed description in Hungarian by Demeter, 2010b), and by the Vancouver Obsessive Compulsive Inventory (VOCI) (Thordarson et al, 2004). In addition, we administered the following instruments: the Hamilton Rating Scale for Depression (HAM-D, 21-item) (Hamilton, 1960; Warren, 1994) to assess the severity of depression, the White Bear Suppression Inventory (WBSI) (Wegner & Zanakos, 1994) to establish the level of thought suppression, and the Spielberger State and Trait Anxiety Inventory (STAI) (Sipos, 1978; Spielberger, Gorsuch, & Lushene, 1970; Spielberger, 1983) to assess anxiety. We excluded participants who met the criteria for severe depression, or for any other comorbid psychiatric diagnosis (Axis I or Axis II) and who had a history of drug abuse or neurological disorder. Regarding medication, two patients had not been medicated for at least three months, eight were taking selective serotonin reuptake inhibitors (seven paroxetin, one citalopram), eight were taking double action noradrenaline and serotonin agents (six clomipramine, two venlafaxine) and two patients were taking serotonin reuptake inhibitors combined with double action noradrenaline and serotonin agents (clomipramin and paroxetin).

The project was approved by the hospital's ethical review board. Patients received a detailed description and explanation of the investigation before they decided to sign the informed consent forms. All patients were assured that participation in the study would not interfere with their clinical treatment. The healthy control group was matched in age and education (see Table 1).

Table 1

Sample demographics and basic assessment results

Characteristics	OCD (*n*=19)		Healthy Control (*n*=19)		Independent t test	
	Mean	S.D.	Mean	S.D.	t	p
Age (years)	36.84	10.09	36.42	9.65	.13	n.s.
Education (years)	13.94	2.81	15	2.47	-1.22	n.s.
Sex (M/F)	13/6		15/4			
DSF	6.23	0.95	6.69	1.01	.28	n.s.
DSB	5.03	1.03	5.23	1.17	0	n.s.
2-back hit %	85	0.15	93	0.11	-1.8	n.s.
2-back correct rejection %	95	0.04	97	0.02	-1.42	n.s.
3-back hit %	73	0.22	84	0.18	-1.53	n.s.
3-back correct rejection %	93	0.03	96	0.02	-2.6	<.01
STAI-T	33.78	8.41	19.00	5.28	6.48	<.001
STAI-S	26.89	9.57	20.21	7.48	2.39	<.05
WBSI	50.66	9.74	41.89	9.77	2.63	<.01
VOCI	78.31	32.50	23.21	12.82	6.87	<.001
Y-BOCS Total	26.31	6.92				
Y-BOCS ORS	13.21	3.59				
Y-BOCS CRS	13.10	4.59				
HAM-D	8.10	3.94				

Note. OCD, obsessive-compulsive disorder; M, male; F, female; Y-BOCS Total, Yale Brown Obsessive Compulsive Scale Total score, Y-BOCS ORS, Yale Brown Obsessive Compulsive Scale, Obsessions-Severity Score; Y-BOCS CRS, Yale Brown Obsessive Compulsive Scale, Compulsions Severity Score; VOCI, Vancouver Obsessive Compulsive Inventory – total score; HAM-D, Hamilton Depressive Rating Scale; STAI-T, Spielberger Trait Anxiety Score; STAI-S, Spielberger State Anxiety Score; WBSI, White Bear Suppression Inventory - total score; DSF, Digit Span Forward; DSB, Digit Span Backward, n.s., not significant.

Experimental design and materials

The retrieval practice paradigm

Materials were the same, and the procedure was similar to that used by Keresztes and Racsmány (unpublished manuscript). Item type was varied within subjects. We used ten categories and six words in each category that is a total of 60 category-word pairs. Words in of two categories were used as fillers. The remaining 48 words (remaining eight categories) were assigned to one of four item types. Four categories were selected randomly to be practice categories for each participant. The other four categories were not practiced. Words within each category were split randomly into two groups. One half of the words (Rp+) in each practiced category was to be practiced during the practice phase, the other half (Rp-) was not. Words in the categories that were not practiced served as baseline items. One half of the words (Nrp+) in each category not practiced served as baseline for Rp+ words, the other half (Nrp-) served as baseline for Rp- words. We used Presentation 14.5 to assign items to conditions, for presentation of stimuli and data recording. All participants performed the experiment on an IBM T40p ThinkPad.

Inventories and scales used

For a short description of the Y-BOCS and HAM-D please refer to Study 3, page 81.

White Bear Suppression Inventory (WBSI)

The WBSI developed originally by Wegner and Zanakos (1994) is a 15-item questionnaire designed to measure thought suppression. The scoring is based on a 5-point Likert scale from strongly disagree (1) to strongly agree (5). Higher scores indicate greater tendencies to suppress thoughts (max. 75 points). We used the Hungarian unpublished translation by Racsmány.

Spielberger State and Trait Anxiety Inventory (STAI)

The STAI was originally developed by Spielberger, Gorsuch and Lushene (1970) to measure anxiety. Contains a total of 40 items with two subscales: The first subscale (STAI-S, 20 items) measures state anxiety, the second measures trait anxiety (STAI-T, 20 items). The scoring is based on a 4-point Lickert scale from not at all (1) to very much (4). The total score

is based on the sum of the points obtained on the two subscales (max. 160 points). We used the Hungarian version of the inventory (Sipos, 1978).

Vancouver Obsessive Compulsive Inventory (VOCI)

The VOCI developed by Thordarson et al. (2004) uses 55 items to assess the degree of symptom severity on six dimensions: contamination, checking, obsessions, hoarding, just right and indecisiveness. Scoring is based on a 4-point Likert scale, from not at all (0) to very much (4). We used our not published Hungarian back translated version.

Assessment of short term and working memory

Digit Span Forward (DSF) and Digit Span Backward Task (DSB)

We used the Hungarian version of the DSF and DSB Tasks as measures of verbal short-term memory (Racsmány, Lukács, & Pléh, 2005). In both tasks a series of digits are presented orally by the examiner at a rate of one digit per second. The digits are to be repeated by the participant in the same (forward span) or in the reverse order (backward span). In our version each trial consisted of four series of equal length (three digits in the first trial). A trial was considered successfully completed if the participant reproduced at least two series correctly. In this case the test advanced to the next trial using series that were one digit longer. Digit span was determined by the length of the series in the last trial where the participant could recall at least two series correctly (see Table 1).

Visual N-back Task

We designed visual 2-back and 3-back tasks with digits to measure the updating function of working memory. Each task consisted of 5 blocks with 30 trials. The first block served as practice in both the 2-back and the 3-back tasks. In these practice block participants were given feedback about correct hits, false alarms and misses. After each block participants had a short break. In each trial, lasting 2000 ms, a digit, randomly sampled from 1-9, appeared in the center of the screen for 700 ms, followed by a blank screen for 1300 ms. Participants had to press the space bar on the keyboard if the digit on the screen was identical to the digit seen two trials before (in the 2-back task), or the one three trials before (in the 3-back task).

Procedure

"In the study phase, participants were presented all 60 words paired with their category label. Each pair was shown once for 5000 ms in the center of the screen with the category label on the left and the category member on the right. Participants were instructed to memorize the words with the help of the category label. Presentation of the pairs was pseudo-randomized with the constraint that two words belonging to the same category could not appear consecutively.

The practice phase consisted of three blocks, each containing 18 practice trials. Each block consisted of 12 trials with Rp+ items and six trials with fillers. The first and the last two items in each series were filler items. The order of the rest of the items was pseudo-randomized with the constraint that two consecutive trials never involved members of the same category. In each trial, the category label of the target word plus a two-letter stem cue for the target word appeared in the middle of the screen." (Keresztes & Racsmány, unpublished manuscript). Participants were instructed to say aloud the corresponding target. They had 6000 ms in the first block and 4000 ms in the second and third block to answer. Answers were recorded with a voice-key, and the correctness of the answers was manually checked by the experimenter after each session.

The three practice blocks followed each other in a repeated spaced retrieval schedule in order to increase the effect of practice (see Karpicke & Bauernschmidt, 2011). We introduced three, and six minutes of delay filled with simple arithmetic (adding or subtracting three-digit numbers randomly generated by the experimental software), before the second, and third practice block and a 5 minute delay before the final test, respectively.

"The final test phase consisted of two blocks. In order to avoid output interference (see Anderson, 2003) Rp- items and their controls (Nrp- items) were tested in the first block, followed by Rp+ items and their controls (Nrp+ items) in the second block. Items were randomly intermixed within blocks (Camp, Pecher, & Schmidt, 2007). The use of different control items for Rp+ and Rp- items was necessary to circumvent baseline deflation (see Anderson, 2003). Both blocks started and ended with two filler items. Trials were the same as in the first retrieval practice block except that the category-plus-word-stem cue contained only a first-letter stem of the category member." (Keresztes & Racsmány, unpublished manuscript).

RESULTS

The effect of practice on final test performance

Statistical analyses were performed using mixed analysis of variance (ANOVAs) with an alpha level set at .05, one-tailed t-tests and bivariate correlation (Pearson correlation coefficient).

We conducted a mixed design ANOVA on recall data with item type (Rp+, Rp-, Nrp+, Nrp-) as a repeated measures variable, and group (control vs. OCD) as a between subject variable. Item type had a significant main effect on final recall, $F(3,108) = 49.54$, $p < .001$, which was overall due to the fact that practiced items were better recalled than their baseline in both, the control group, $t(18) = 6.12$, $p < .001$, $r = .82$, and the OCD group, $t(18) = 8.52$, $p < .001$, $r = .90$. Item type did not interact significantly with group, $F(3,108) = .74$, *ns*. Mean recall performances at the final test are shown in Table 2.

Table 2

Recall Performance (In Percent Recalled) at Final Test for the Four Item Types in the Control and the OCD group

		Item type			
Group	N	**Rp+**	**Rp-**	**Nrp+**	**Nrp-**
OCD	19	.72 (.17)	.40 (.17)	.38 (.16)	.40 (.15)
Control	19	.68 (.18)	.38 (.18)	.38 (.16)	.45 (.19)

Note. Rp+: Practiced words from practiced categories, Rp-: unpracticed words from practiced categories, Nrp+: words from unpracticed categories used as baseline for Rp+ words, Nrp-: words from unpracticed categories used as baseline for Rp- words. Standard deviations are shown in brackets.

RIF

To detect a RIF effect, we performed paired-samples *t*-tests (one-sided) for the OCD and the control group separately, contrasting Rp- recall with Nrp- recall. We found a medium-sized RIF effect in the control group, $t(18) = -1.73$, $p = .05$, $r = .38$, but absolutely no effect in the OCD group, t(18) = 0, r = 0 (see Figure 1). There was no significant correlation between the RIF effect and the STAI, VOCI, Y-BOCS scores, neither with the short term, working memory scores in the OCD group. In the healthy control group we found a significant positive correlation just between the RIF effect and the WBSI scores, r= 0.52, p<.05, similarly, WBSI scores and the percent of correct rejections on the two back working memory task, r=.45, p<.05.

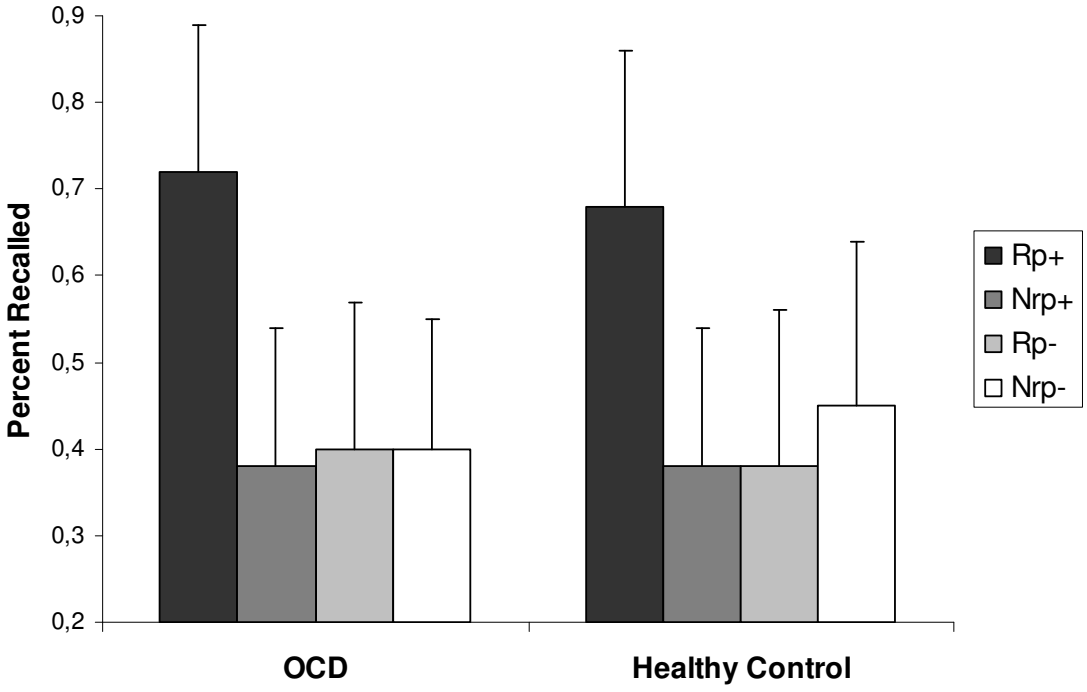

Figure 1. Mean percentages of exemplars recalled by the OCD and Healthy control group

Note. Error bars show standard deviations.

Short term and working memory

We performed independent *t*-tests to compare the OCD and the control group performance on these probes. There was no significant difference on the DSF , $t(36) = .28$, $p > .05$, $r = .05$, and DSB tasks, , $t(36) = 0$, $p > .05$, $r = 0$, neither in hit rates in the two-back task , $t(36) = -1.8$, $p > .05$, $r = .29$, nor in hit rates in the three-back task , $t(36) = -1.53$, $p > .05$, $r = .25$, just on the percent of correct rejections on the three back task , $t(36) = -2.6$, $p = .01$, $r = .40$.

CONCLUSION

Our goal was to acquire evidence regarding the role of executive functions in RIF. For this purpose near the healthy control group we used a clinical sample (OCD) in which executive, mainly inhibitory, impairment constitutes the core cognitive deficit. Results showed that retrieval of some memories led to enhancement in both groups, but forgetting of related memories (RIF) occurred only among controls. This finding was not due to different levels of anxiety, working or short term memory capacity and symptom severity. We did not find relations between RIF and trait or state anxiety measured by the STAI and thought suppression capacity measured by the WBSI in the OCD group. There was no significant correlation between RIF and working, short term memory scores in either of the groups.

Interestingly, we can see a different pattern regarding the recall of NRP- (control items for Rp- items) and NRP+ (control items for Rp+ items) items between the two groups. In the final recall we test first the NRP- items, then the NRP+ items to avoid output interference. The healthy control group recalls more NRP- items then NRP+, while in the OCD group there is no difference, which could mean that the patients are not sensitive for output interference. We suggest that the lack of RIF might be explained by the dysfunction of conflict detection processes observed in OCD.

Chapter 7. Discussion, conclusions and further directions

7.1. Discussion and conclusions

Our main aim with this thesis was to figure out and define the core cognitive deficits in OCD using neuropsychological and cognitive experimental psychological methods. By doing so we intended to develop better understanding of the clinical symptoms, the persisting and recurrent thoughts, and the repetitive and compulsive actions.

Earlier neuropsychological studies with tasks tapping short-term memory and executive functions in OCD have produced inconsistent results (for reviews see Chamberlain et al., 2005; in Hungarian Demeter et al., 2008; 2010a; Greisberg & McKay, 2003; Kuelz et al., 2004; Olley et al., 2007;). This could be attributed to the facts that the executive system is not unitary and the different methods used to evaluate executive functions require different cognitive processes. According to Miyake and collaborators (2000) traditional neuropsychological executive tasks load on three main central executive components: inhibition, modality specific updating-monitoring and shifting. The aim of our study (Study 1, Thesis I) was to assess the level of short-term memory and executive functions in a properly diagnosed clinical sample of OCD patients compared to healthy control subjects and to describe the distribution of patients in different impairment ranges for all functions. A further goal was to clarify the relationship between symptom severity and cognitive impairments and to integrate the results in a coherent explanation model. In our study the OCD group performed within the range for healthy adults in the short term memory tasks (Digit Span Forward and Backward Task), while they produced severely impaired performance in executive tasks assessing inhibition (Stroop Task) and shifting (WCST). The increased reaction times on the interference condition in the Stroop task as well as the higher number of perseverative errors in WCST could be interpreted as a consequence of impaired inhibitory mechanisms. We argue that set-shifting also requires the ability to inhibit previously acquired rules, a process mediated by the orbitofrontal cortex (Chamberlein et al., 2005). There is also a relation between symptom severity and performance scores, patients with more severe symptoms committed more perseverative errors.

Our findings support the view that the updating component of the executive system seems to be intact in OCD while the inhibition and shifting components are altered. The failures of inhibition mechanism could explain this observation. This interpretation is in line with the neuropsychological model of OCD where the deficits of cognitive and behavioral

inhibition are responsible for the main cognitive findings of this disorder (Chamberlein et al., 2005).

We think, as Ellis (1996), that the executive functions play an important role in the realization of delayed intentions, in PM performance. Although execution and cancellation of intended actions are evidently important functions from the perspective of OCD symptoms, they have rarely been studied in the field.

In two consecutive experiments (Study 2 and 3) we have demonstrated the impairment of PM functions in event-based task in OCD (Thesis II). There are just a few studies with OCD patients or with subclinical groups with dominant checking symptoms or obsessive tendencies in the domain of PM (Cuttler & Graff, 2007; 2008; 2009; Harris et al., 2010; Jelinek et al., 2006; Marsh et al., 2009). Most of them point toward an impaired event-based and intact time-based PM performance. Contrary to previous interpretations we argue by an overactivity of the PM system in OCD.

In our first study (Study 2) we applied the paradigm elaborated by Burgess et al. (2001). In this experiment we found that OCD patients slowed down on the ongoing task in both the expectation condition (in which participants were told that PM stimuli might occur but none actually did) and in the execution condition (in which participants were told that PM stimuli might occur and they did) compared to the baseline. We propose the occurrence of extra monitoring activity as probable cause for this finding. The PM instruction produced an extra monitoring activity for the OCD patients that resulted in a more active search for PM cues. It also caused higher reaction times on the ongoing task in the expectation and execution conditions. The higher latency and lower accuracy scores in the experimental trials compared to the control trials are evidence of monitoring activity (see Guynn, 2003; Kliegel et al., 2001, 2004; Marsh et al., 2005). This interpretation is aligned with previous findings obtained with OCD patients demonstrating overactive performance in action monitoring tasks (Johannes et al., 2001; Ursu et al., 2003). Monitoring as the component of the executive system is the central factor of the two dominant explanations of PM. According to the multiprocess model (Einstein et al., 2005; McDaniel & Einstein, 2000; McDaniel et al., 2004), PM retrieval is mediated by automatic and strategic processes. Monitoring is a strategic process by which subjects can scan the environment and look for targets indicating the execution of the relevant intended actions. The PAM model (Smith, 2003; Smith & Bayen, 2004) is another approach in which monitoring as a possible preparatory attentional process also has an important role in detecting the relevant target events that indicate the appropriate time for PM actions. According to this model, PM retrieval is mediated by non-automatic preparatory attentional

and retrospective memory processes (Guynn, 2008). Our result - that OCD patients produced extra monitoring activities in a PM task - is explainable in both models as the over-activation of controlled attentional processes.

We have designed our second study (Study 3) to acquire more evidence about the over-monitoring hypothesis in OCD. A modified PM task was used with minimal memory load suitable for patients under medication and with the goal of simulating a real life situation, where following a successful response to a relevant target, the response must be inhibited for the same target on the next encounter with it. This task compared to our previous experiment required a more intense monitoring activity from subjects concerning their own actions, making it appropriate for analysing the monitoring activity through reaction times and errors made.

We have found not just similar data regarding reaction times with our previous experiment, but also significant differences in error patterns. The significantly higher rate of false alarm type errors may reflect the overactivity of the PM system and also a response inhibition deficit (Chamberlain et al., 2005). We argue that over-activated PM intentions go together with a response inhibition deficit, and that these two factors together contribute to the higher rate of false alarms. Another important result supporting our view is that patients who achieved higher scores on the PM subscale of the PRMQ made significantly more errors on the PM task. Taking together the hit rates on the PM task and the reaction time scores on the ongoing task in the execution condition, it can be concluded that OCD patients' performance can be explained by over-monitoring for PM cues.

Another frame for interpretation is the 'gateway hypothesis' suggested by Burgess and colleagues (Burgess et al., 2003; Burgess et al., 2005; Burgess et al., 2007a, 2007b, 2007c). This theory makes a difference between stimulus-oriented (SO) and stimulus-independent (SI) attending (McGuire et al., 1996). The first is involved in the processing of the present sensory input, while the second is required in the realization of self-generated or self-maintained thoughts. Our results suggest that OCD patients might have difficulties in SI attending, which also has a secondary negative effect for SO attending. The PM task required the maintenance of an intention for a longer period and at the same time the inhibition of every second PM response from the subjects while they were involved in the realization of the ongoing task. The task of the present study required a constant switch between SO attending (ongoing activities, responding to ongoing or PM stimuli) and SI attending (when no PM stimuli were displayed). It could be that maintenance of the PM intention requires extra SI attentional processes, which impairs the execution of the ongoing activities (SO attending) in OCD.

Following the successful execution of a specific PM action, OCD patients may not cancel the activation of previous PM intention, and these results in a constant search for environmental PM cues and will cause a higher rate of false alarm type errors (responding to a PM cue when not supposed to). Further experimental work is required to confirm these assumptions and to clarify the mechanism involved.

The relationship between monitoring functions of PM cues and OCD symptoms is also interesting from the perspective of neuroimaging studies. A series of studies found evidence that the rostral prefrontal cortex (BA10) is involved in PM (Burgess et al., 2001; Burgess et al., 2003; Simons et al., 2006). The neuroimaging research of OCD gave a further hint that PM functions could be relevant in an OCD endophenotype, as it was found that those brain areas that are involved in PM are among the affected brain structures in OCD. There are structural neuroimaging studies showing that the volume of the orbitofrontal cortex is significantly reduced (Atmaca et al., 2007; Choi et al., 2004; Kang et al., 2004; Szeszko et al., 1999), and findings near the volumetric increase of the thalamus in OCD (Atmaca et al., 2006; Gilbert et al., 2000). We also know that the thalamus is involved in the anticipatory attentional processes and in the monitoring of self-generated actions (Blakemore, Rees, & Frith, 1998; Portas et al., 1995).

Without proper neuroimaging studies we just hypotheses that in OCD the activity in the thalamus and dlPFC is at the same level when they only expect a PM cue than when they execute a PM action.

Based on all these results we think that PM function training in cognitive-behavioral therapy protocol could be beneficial to ameliorate main clinical symptoms and may contribute to the better everyday well-being of the patients.

Many factors – such as motivation, stress, the properties of the PM cues, the characteristics of the ongoing task, planning and individual differences – influence the successful performance on PM tasks. In case of memory retrieval there is an impressive amount of data demonstrating that *interference* plays also an important role in forgetting (see Anderson & Neely, 1996; Postman, 1971). In today's memory research there is still an active debate about how we can overcome interference and resolve competition between similar traces when retrieving specific target memories. According to Anderson (2003) the need to resolve interference during retrieval induces executive control processes that overcome interference through inhibition of the interfering non-target memory. By to this view this inhibitory mechanism answers the question of why we forget previously studied information when we retrieve related items from memory, a phenomenon known as the RIF (Anderson,

Bjork, & Bjork, 1994), which was often studied by the retrieval practice paradigm (Anderson, 2003). There is evidence questioning this account and offering non-inhibitory explanations for RIF (see Camp et al., 2007). Researchers consider the retrieval practice effect a short rather then a long term effect (Anderson, 2001; Saunders & MacLeod, 2002). We know that the operation processes operating during sleep play a crucial role in the consolidation of episodic memories (Conwey, 2009; Williams, Conway & Baddeley, 2008) and according to Norman, Newman & Detre (2007) it could be that REM sleep modulates also the inhibitory patterns as well. MacLeod and Macrae (2001) found evidence that a 24 hour delay between initial encoding and retrieval practice just diminished but could not eliminate forgetting. It is still unclear if the suppression effects due to selective practice are lasting for seconds, creating just a short term reduction in the activity level of competing responses or are long term effects, which determines the durable accessibility of items from memory. We think that this is an important aspect in the understanding of OCD symptomatology

We have demonstrated that the RIF effect persists in long term in healthy subjects, after 12 hours if there is no active rehearsal and a period of nocturnal sleep is included before the surprise delayed recall (Study 4, Thesis III). In the absence of rehearsal the retrieval-practice effects began to dissipate after a retention period of just 1 hour (Morning no-sleep group, Experiment 2). In one experiment just mentioned in our study we found that if there is rehearsal during the retention interval, then retrieval practice effects will be present also after 12 hours (with no period of sleep). According to the *episodic inhibition account* (Racsmány & Conway, 2006) in the retrieval practice paradigm the study of item pairs gives rise to the formation of an episodic memory and the practice phase establishes a pattern of activation and inhibition over these memories. On the final recall then this pattern of activation-inhibition will mediate access to memories. It seems likely that the opportunity for interference by new memories was greater in our no-sleep than in our sleep-groups, and, consequently, integration may have been attenuated in the no-sleep relative to the sleep groups. We can conclude that the greater degree of integration of memories in the sleep groups underlies the observed retrieval-practice effects.

Demonstrating these long term effects of selective retrieval with healthy subjects we were able to use the paradigm for the study of inhibition mechanism involved in OCD. From previous studies we know that the patients manifest problems in the use of organizational strategies during memory encoding and have difficulties in conflict resolution situations (see e.g., Savage et al., 1996; Kuelz, et al., 2004). For the cognitive profile of OCD it seems essential the overactiveted mechanism involved in conflict detection, monitoring and

inhibition of competing information. We thought that the study of retrieval memory inhibition in OCD could furnish further evidence about the conflict detection processes involved and also about executive deficit (Study 5, Thesis IV). Chamberlain et al. (2005) assumes that deficits of inhibition mechanism are responsible for the main symptoms and neuropsychological profiles in OCD. Impaired performance was demonstrated on a series of different inhibition paradigms as the Stroop Task (e.g., Martinot et al., 1990), the Go/NoGo Task (Bannon et al., 2002; Penades, et al., 2007; Watkins et al., 2005), the antisaccade task (Maruff, et al., 1999; Spengler et al., 2006; Tien et al., 1992) in this disorder.

The OCD patients do not show the RIF effect, whereas we found similar practice effects in both the control and the OCD group. According to our findings this is not affected by the level of state anxiety, working memory capacity or short term memory capacity. Contrary to the findings of Koessler et al. (2009) who argue that stress might eliminate RIF in healthy adults by temporary suspending the inhibitory mechanism involved, we haven't found relations between RIF and trait or state anxiety measured by the STAI in the OCD group. Levy and Anderson (2008) and Aslan and Bäuml (2010) argues that working memory capacity positively correlates with RIF. We know from previous research that OCD patients manifest poorer performance on tasks which require updating of the executive system, such as the *Letter Memory Task* (e.g. Morris & Jones, 1990), and the *N-back Task* (e.g. van der Wee et al., 2003). We haven't found significant difference between the two groups regarding the hit rates on the N-back tasks and there was no significant correlation between RIF and working, short term memory scores in either of the groups.

The different pattern regarding the recall of NRP- (control items for Rp- items) and NRP+ in the two groups could mean that the patients are not sensitive for output interference. Most probably, the lack of RIF might be explained by the dysfunction of conflict detection processes observed in OCD.

Regarding the findings from cognitive neuroscience there is also a plausible connection between the cortical structures involved in OCD and RIF. In OCD there is evidence supporting the hyperactivity of the lateral orbitofrontal cortex (lOFC) and the hypoactivity of the medial OFC (mOFC) (for review see Milad & Rauch, 2012). In this context another important structure which is also affected in OCD is the dorsal anterior cingulated corex (dACC), involved mainly and in all situations which implicate cognitive conflict resolution and error detection (Bush et al., 2002; van Veen & Carter, 2002). There are studies showing the hyperactivity of the dACC in the incongruent compared to the congruent conditions (e.g. Fitzgerald et al., 2005; Maltby et al., 2005; Page et al., 2009) in inhibition paradigms with

OCD patients. By Milad and Rauch (2012) it could be that the hyperactivity of the dACC contributes to the persistence of error signals which produce the obsessive thoughts in OCD.

In an fMRI study Kuhl, Dudukovic, Kahn, and Wagner (2007) found evidence that the repeated retrieval of target memories reduces the activity in the control network at the level of ACC and dorso- and ventrolateral PFC, structures important in detecting and resolving interference. The magnitude of reduction of PFC activity across repeated retrieval attempts of a target memory was associated with increased forgetting of interfering non-target memories at a final test. Accordingly a functional MRI study demonstrated that when memory competition is successfully resolved the activity of the left medial and left lateral PFC, as well as activity in the left ACC is reduced, showing that the frontal structures are important not just in target memory selection but also in inhibition of related memories (Wimber, Rutschmann, Greenlee, & Bäuml, 2009).

Based on all these findings a plausible assumption would be that the RIF effect is absent in OCD patients due to inappropriate conflict resolution processes during retrieval of competing memories maintained by the constant hyperactivity of ACC and prefrontal structures. Seemingly it is like a paradox, the more recruited these structures are, the patients are less able to inhibit irrelevant and competing memories. Although there is no way to say more on this issue without proper neuroimaging studies it seems a plausible explanation to our results from a different perspective. Further experimental and neuroimaging research is need to clarify and confirm the outlined assumptions.

Our data support the executive system deficit in OCD and we argue that an inhibition impairment could contribute to the overactivity and cancellation deficits observed in the PM system and to the altered recall of episodic memories. The observed clinical symptoms could be explained in this interpretation framework and a substantial amount if neuroimaging studies support the altered function of different cortical structures involved in the realization of inhibition processes (Fitzgerald et al., 2005; Maltby et al., 2005; Milad & Rauch, 2012; Page et al., 2009).

There were some limitations to our studies. First we used a heterogeneous group of patients and did not use subgroups. Second, the majority of the patients were under medication during the studies. Third, we based our conclusions on the few neuropsychological tasks and experimental paradigms selected for these studies. Further research is needed to clarify the exact nature of inhibitory executive processes, respective PM functions, their relations and contributions to the cognitive neuropsychological profile and symptoms of the disorder.

7.2. Further directions

We think that in OCD the domain of executive function research requires substantially greater sample and hopefully the upcoming research will describe the different neuropsychological profiles of different subgroups, indentifying also the impaired main cortical areas involved.

If we comprehend OCD as a disorder in a continuum running from the very severe cases to the subclinical range, the studies focusing on the first degree relatives and on the identification of *endophenotipic markers* represent a great step forward.

We think that by selecting a few very simple cognitive tasks where the impairment of OCD is well documented and the involved functions are clearly defined (e.g., Stop Signal Task; ID/ED shift, Visual Working Memory Task) near the usually neuropsychological assessment the use of the *eye tracker methodology* could represent a major step in gathering new information and determining those eye movement parameters that can highly discriminate between OCD and healthy subjects.

There are a lot of open questions also in the domain of PM research. We think that the development and use of paradigms that can discriminate and measure the different PM phases and the functions involved could be a great interest here. There are just a couple of studies and we need further evidence regarding the performance of OCD patients in time and event-based PM tasks.

According to the *gateway hypothesis* (Burgess et al., 2003) we think that is possible that in OCD the maintenance of the intention requires extra SI attentional processes which impairs the execution of the ongoing activities (SO attending). We also think that different subgroups of OCD patients will manifest different performance patterns on PM paradigms and this kind of further research could contribute to the findings of endophenotypic markers in OCD. According to our hypothesis, patients characterized with dominantly obsessive symptoms will have difficulties in SI attending while patients with dominantly compulsive symptoms will have difficulties with SO attending. These assumptions need further research and evidence.

As far as we know we are also the first in demonstrating the absence of RIF effect in OCD, but the exact nature of the mechanism involved is not clear and further experiments are required.

Currently, the treatment of OCD turns its focus from the use of irreversible surgical methods (e.g., anterior cingulotomy) toward reversible methods such as the Deep brain stimulation (DBS). Neuropsychological assessment could have a crucial role in the evaluation

of patients' cognitive abilities before and after the surgery, thereby contributing to the determination of its effectiveness, and to the elaboration of standard assessment protocols.

We also think that research regarding the description of different connections among goal attainment, reward and PM system could be of critical importance and could furnish further data to our modified PM model together with the neurobiological research. This clinical domain combined with experimental cognitive psychology methodology offers a lot of open and exciting questions and further research is needed to clarify it and to integrate main findings in the cognitive psychotherapy of the disorder.

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