Budapest University of Technology and Economics
PhD School in Psychology – Cognitive Science

Albu Mónika

NEUROPSYCHOLOGICAL EXAMINATION OF LATERALIZED EXECUTIVE FUNCTIONS DURING MEMORY RETRIEVAL

Supervisor:

Racsmány Mihály, PhD

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INTRODUCTION

In the past few decades, the nature of the executive function and its neural implementation has arisen as one of the most important issues in understanding higher order cognitions. Despite the substantial number of studies on the topic, the concept of executive function remains elusive. There is, however, an emerging consensus in the literature that fractionating the early conception of a unitary 'central executive' is necessary (Baddeley & Hitch, 1974; Baddeley, 1986). Recent models have suggested a view of the executive functions as a conglomerate of largely independent, but interacting, control processes such as interference resolution, attention-shifting, updating, and inhibition (Johnson, 1992; Baddeley, 1996; Fuster, 1997; Smith & Jonides, 1999; Miyake et al., 2000; Friedman & Miyake, 2004; Marklund et al., 2007). A common characteristic of these models is that the postulated executive subprocesses are considered to be domain general in the sense that they play an important role in a broad range of distinct cognitive domains (e.g., attention, working memory, episodic long-term memory) (Baddeley, 1996; Marklund et al., 2007). In the memory domain, executive processes are particularly involved in working memory, metamemory, generation of memory cues, monitoring contextual features such as temporal order, strategic memory retrieval, and memory inhibition (see Shimamura, 1995).

The contribution of inhibitory processes to cognitive control and executive functions has received increased interest during the last few decades. In classical neuropsychological cases, a deficit of inhibition was described in frontal lobe patients since the famous case of Phineas Gage (Harlow, 1868; Milner, 1964; Damasio, 1996; see Stuss, 1991, for review). Lurija (1966) also decribed particular signs of disinhibition (perseverations, stereotypes, behavioural disinhibition, etc.) in patients with large frontal lobe lesions. Overall, neuropsychological researchers have suggested that the deficit of inhibitory mechanisms is specifically associated with frontal lobe lesions (e.g. Dempster, 1995; Shallice, 1988; Shimamura, 1995; Conway & Fthenaki, 2003; see however Andres, 2003, 2004 for critique), but still remain a debated question which specific brain regions are responsible for distinct inhibitory functions.

The automatic and intentional inhibitions play an important role in executive processes and emotions may interfere with the effectiveness of this executive system. There has been considerable interest in research into inhibitional biases for threat information in anxiety because recent cognitive theories have proposed that such biases may play a key role in the development and maintenance of clinical anxiety states and may cause pseudo-executive symptoms.

Another major issue concerning the neural basis of episodic memory is the separate roles of the two hemispheres in episodic memory retrieval and executive processes. Most theories of lateralization posit some combination of material-specificity and process-specificity; however, the amount of these factors and their

interaction remain unclear. Lateralized executive functions of the two hemispheres in memory retrieval are explained by various models. The left-right contrast is emphasized in the well known Hemisphere Encoding and Retrieval Asymmetry model of Tulving, Kapur, and Craik (1994) proposing, that left PFC have a greater role in encoding information into memory, whereas the right PFC is more engaged than the left in retrieval. Recently developed new hypothesis, like the "cortical asymmetry of reflective activity" (CARA) model and "production-monitoring" hypothesis proposes alternative explanations for hemispheric dissociation. The CARA model states that the left PFC is more involved in systematic retrieval, while the right PFC is more active in heuristic retrieval (Nolde, Johnson, & Raye, 1998b). The "production- monitoring" hypothesis proposes that the left PFC is primary involved in semantically guided production of information, while the right PFC is more active during monitoring processes (Cabeza, Locantore, & Anderson, 2003).

GOALS

The main purpose of the present dissertation was to examine the role of the two hemispheres in various executive and memory processes.
Section 2.1 - Section 2.4 from the dissertation aimed to investigate the role of prefrontal cortex in inhibitory control processes, with the help of four widely used experimental procedures, testing for automatic /intentional attention and memory inhibitory processes.

The purpose of the Section 2.5 and Section 2.6 was to investigate the effects of anxiety related emotions on executive processes by comparing emotional inhibition performances of persons with frontal lobe injury and persons with generalized anxiety disorder (GAD).

The main purpose of the Section 3 was to examine the role of the two hemispheres in executive and memory processes. We used a lesion study designed in a way to contrast the existent hypotheses regarding the role of the two hemispheres in episodic retrieval processes.

Section 4 aimed to examine the relation between the different executive components and episodic memory functions, trying to find common executive components in classic neuropsychological tests and in newly developed, experimental memory- and executive tasks.

Finally, Section 5 summarizes the experimental and clinical results, emphasizing the different and separate role of the two hemispheres and tries to provide an explanatory-integrative model of executive functions involved in episodic memory retrieval.

NEW SCIENTIFIC RESULTS

THESIS 1

Right frontal cortex has a fundamental role in intentional inhibitory processes (1, 2, 3).

An influential recent theory by Aaron et al. (2004) points to the right inferior frontal cortex as the center of inhibitory executive system.

Involving three brain damaged patient groups with various localization of the lesion site, we selected four widely used experimental tasks assumingly involving inhibitory processes. The four tasks were: the Stroop task, go/no-go task, directed forgetting task (list method) and selective retrieval practice task for retrieval induced forgetting effect. According to our results, patients with right frontal lesion produced reversed inhibitory effect on intentional forgetting task, and produced no inhibitory effect on the Stroop task and on the go/no-go task, while produced a normal level of retrieval induced forgetting. Left-frontal patients produced larger inhibitory effects compared to the right-frontal patients on all intentional tasks, although these effects were attenuated compared to the healthy control group. Finally, the patient group with temporal lobe lesion produced a comparable to normal level of inhibition on all tasks and lateralization of the lesion size had no effect on the results. These results support the assumption that the right frontal cortex has a fundamental role in intentional inhibitory processes.

THESIS 2

Inhibitory processes can be disrupted not only by frontal lobe injuries but by interfering anxiety related emotions too, resulting in selective attentional and memory inhibitional biases (4, 5, 6, 7).

It has been theorized that attentional bias for emotional stimuli is a component of a variety of anxiety disorders. We used the emotional Stroop task and a modified directed forgetting tasks to clarify the

effects of attentional and inhibitional biases on the processing of emotionally threatening material in persons with generalized anxiety disorder (GAD) and in frontal lobe injured patients. The data demonstrated that both frontal lobes injured and GAD groups have difficulties in inhibiting the irrelevant information, but in GAD group this effect was selective toward anxiety-related words. GAD patients produced intentional memory inhibition bias, similarly to the frontal lobe injured group, but in GAD group this bias was selective toward anxiety related stimuli, showing no intentional forgetting effect when the words designated 'to-be-forgotten' were emotionally salient.

These results support the assumption that the frontal cortex has a fundamental role in inhibitory processes, and that these inhibitory processes can be disrupted by interfering anxiety related emotions.

THESIS 3

The "production-monitoring" hypothesis is more appropriate in explaining the effect of frontal lobe lesion on memory performances, whereas the heuristic-systematic hypothesis is more suitable to explain the effect of temporal lobe lesions in episodic memory (8,9).

Our study was designed to contrast the existent hypotheses regarding the role of the two hemispheres in episodic retrieval processes. The widely known hemispheric encoding/ retrieval asymmetry (HERA) model emphasizes the role of the left hemisphere in encoding, whereas the right hemisphere is considered to be more active during

episodic retrieval. The so-called "systematic–heuristic" hypothesis states that the left PFC is more involved in systematic retrieval, whereas the right PFC is more active in heuristic retrieval. The "production-monitoring" hypothesis proposes that the left PFC is primary involved in semantically guided production of information, whereas the right PFC is more active during monitoring processes.
We used 10 verbal and visual recall and recognition tasks loading various processes of production, monitoring, analytical and heuristic functions. Frontal and temporal lobe patients with left or right-sided lesions were included in this study. The results support the assumption that the "production-monitoring" hypothesis is more appropriate in explaining the effect of frontal lobe lesion on memory performances, whereas the heuristic-systematic hypothesis is more suitable to explain the effect of temporal lobe lesions in episodic memory.

THESIS 4

The 7 Courses Memory Test has proved to be adequate to quick screening as well as to detailed analysis of memory- and executive components (10, 11, 12).

The 7 Step Memory Task has been designed to examine visual-spatial memory components and their interactions in people with acquired brain injury and it provides a scoring method for the temporal organization of

memory items, effect of stimuli frequency and proactive interference. Various groups of normal controls and brain injured patients with different lateralization and localization (bifrontal, left- and right frontal, left- and right posterior, left- and right temporal) were examined. In summary, the data show that as a result of both qualitative and quantitative analysis, the healthy and brain injured persons are well differentiated by each measures of the test. Furthermore, groups with different lateralization can be separated based on their quantitative scores (hits and false alarms in the 7 "courses") and specific error types: the patients with right hemisphere injury showing more impaired performance in comparison with patients with left hemisphere injury. Additionally, since specific error types indicated a dysfunction in the executive system, using PCA we defined two executive indices: Inhibition and Self-monitoring. The comparison of these two indices indicated that the right hemisphere injured patients are clearly more impaired and showed no inhibition and self-monitoring in comparison with the left hemisphere injured patients.

THESIS 5

We propose an integrative-executive model with five separable executive processes in episodic memory retrieval: Inhibition, Updating, Shifting, Monitoring and Production (1, 2, 3, 8, 9, 10, 11, 12, 14).

The executive components model of Miyake et al. (2000), and the production/ monitoring factors (Cabeza et al., 2003) were used in

several clinical and correlational studies to examine the supposedly different executive load of episodic memory tasks and its relation with the clinically used neuropsychological tests. First, we have identified some of the executive processes and marshaled evidence for their relationship to specific frontal regions. Five clear separable executive processes were defined with correlation and PCA analyses: Inhibition, Updating, Shifting, Monitoring and Production (strategy generation).

Summarizing the results (Section 2. – Section. 4.), they provide evidence for an anatomically and functionally discrete cognitive architecture to the frontal lobes (see Table bellow). We moved from comparison of frontal versus posterior lesions to the standard anatomical classification within the frontal lobes: right frontal, left frontal, and bifrontal. Two components of our executive model is dependent on right frontal lobe functioning: the Inhibition and Monitoring components. Our studies provided clear evidence for the role of the right prefrontal cortex in intentional inhibition and in monitoring processes. The other three components – Updating, Shifting and Production- were not that meticulously studied than Monitoring and Inhibition, but our lesion studies provided evidence for the left frontal involvement in the Production factor and the role of bifrontal areas in the Shifting and Updating factors.

Inhibition	Monitoring	Shifting	Updating	Production
Right Frontal Cortex		***Bifrontal Cortex***		***Left Frontal Cortex***
Stroop Error Interf.I.	IRN-verbal	BADS-I	Stroop RT Interf.I	SCR-verbal
	IRN-visual	+/- task		SCR-visual
Go/no-go RT	CRN-visual	CCR-visual	n-back	ACR-verbal
	CRN-verbal		Digit-backward	ACR-visual
DF cost	CCR-verbal		SCR-verbal	
7Courses Inhibition I.	ACR-verbal		SCR-visual	
	ACR-visual		CRN-verbal	
	7Courses Self-monitoring			
	BADS			

Note: I: Index; DF: Directed Forgetting; Interf.: Interference; RT: Reaction Time; ACR: Associative-cued recall; SCR: Stem-cued recall; CRN: Context recognition; CCR: Context-cued recall, BADS: Behavioral Assessment of Dysexecutive Syndrome; BADS-I: BADS- Rule Shifting Subtask.

Summarizing the findings from previous sections, we tried to propose a possible integrative-executive model, but wishing to leave open to empirical investigation the question whether the organization is hierarchical, with one or more subsystems dominating, or whether a more heterarchical structure is involved. Regardless, since lesion studies indicate which regions are necessary for a function, these results stand as a framework for more localized patient and imaging studies in the future.

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