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**BEHAVIOURAL AND ELECTROPHYSIOLOGICAL INDICES OF EXECUTIVE
FUNCTIONS IN AGEING AND IN PARKINSON'S DISEASE**

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ABSTRACT

Healthy ageing and Parkinson's disease are both characterized by different changes in the prefrontal cortex and in dopaminergic functionality. Working memory and feedback processing have been related to the dopaminergic activity in the prefrontal cortex (Hämmerer & Eppinger, 2012; Bäckman et al., 2010-2008; Bäckman & Farde, 2005). The aim of the three studies presented in this thesis was to examine if, and how, these two executive functions change in ageing and in Parkinson's disease patients under pharmacological treatment. In detail, a first study investigated executive attention and inhibitory control, top down components of working memory, with the aim to explore the management of the information stored in working memory. Feedback processing was instead investigated in the second study exploring the interaction between motivation and cognitive control and, in the third study, analysing the electrophysiological correlates of outcome evaluation in a decision-making task.

Results of the first study highlighted the presence of an age-related decline in top down components of working memory, like executive attention and inhibitory control, in line with findings about age-related vulnerability to interference and decline in WM (Reuter-Lorenz & Sylvester, 2005). In addition, the results of this study showed as medicated PD patients performed like a matched control group of healthy elderly in terms of accuracy, but better in terms of latency.

Results of the second study indicated that feedback processing is preserved in healthy ageing, but impaired in medicated PD patients, in line with previous findings (Kapogiannis et al., 2011; Spaniol et al., 2011; Harsay et al., 2010; Kobayakawa et al., 2010; Bodi et al., 2009; Frank et al., 2007-2004). Results of the third study contributed to increase the knowledge of this impairment showing the presence of abnormal electrophysiological correlates of feedback processing in medicated PD patients.

Taken together, the results presented in this dissertation confirm the presence of specific age-related declines in executive functions (Verhaeghen, 2011), and also suggest that the pattern of performances of medicated PD patients could be compatible with the effect of a dopaminergic "overdose" in executive functions (Vaillancourt et al., 2013), recommending further investigations about the role of dopaminergic treatment in PD patients' cognition.

RIASSUNTO

L'invecchiamento sano e la malattia di Parkinson rappresentano due condizioni in cui la corteccia prefrontale e il sistema dopaminergico vanno incontro a diversi cambiamenti. La memoria di lavoro e l'elaborazione del feedback rappresentano due funzioni esecutive che sono state correlate all'attività dopaminergica nella corteccia prefrontale (Hämmerer & Eppinger, 2012; Bäckman et al., 2010-2008; Bäckman & Farde, 2005). L'obiettivo dei tre studi presentati in questa tesi è stato quello di studiare se, e come, queste due funzioni esecutive vanno incontro a cambiamenti, durante l'invecchiamento sano e in pazienti con malattia di Parkinson. Nello specifico, nel primo studio sono state esplorate le componenti top-down della memoria di lavoro, ovvero la capacità di focalizzare le risorse sull'informazione rilevante e di inibire l'elaborazione di quella irrilevante, capacità essenziali per la gestione di informazioni in memoria di lavoro. L'elaborazione del feedback è stata invece studiata indagando i meccanismi d'interazione tra controllo cognitivo e motivazione nel secondo studio, e analizzando i correlate elettrofisiologici (ERPs) dell'elaborazione del feedback in un compito di decision-making nel terzo studio. I risultati del primo studio hanno mostrato che nell'invecchiamento sano le componenti top-down della memoria di lavoro vanno incontro ad un declino, coerentemente con precedenti evidenze circa l'aumentata sensibilità all'interferenza e la presenza di deficit di memoria di lavoro nell'invecchiamento (Reuter-Lorenz & Sylvester, 2005).

Pazienti con malattia di Parkinson sotto trattamento farmacologico hanno invece mostrato prestazioni comparabili a quelle del gruppo di controllo in termini di accuratezza, ma migliori in termini di tempi di risposta. I risultati del secondo studio hanno inoltre mostrato che mentre nell'invecchiamento sano la capacità di elaborazione del feedback è preservata, questa stessa capacità è compromessa in pazienti con malattia di Parkinson sotto trattamento farmacologico, coerentemente con quanto riportato in letteratura (Kapogiannis et al., 2011; Kobayakawa et al., 2010; Harsay et al., 2010; Spaniol et al., 2011; Bodi et al., 2009; Frank et al., 2007-2004). I risultati del terzo studio hanno contribuito a questa letteratura mostrando la presenza di anomalie nei correlati elettrofisiologici dell'elaborazione del feedback, in pazienti con malattia di Parkinson sotto trattamento farmacologico. In conclusione, i risultati presentati in questa tesi confermano la presenza di specifici deficit a livello delle funzioni esecutive nell'invecchiamento sano (Verhaeghen, 2011) e suggeriscono una compatibilità con l'ipotesi di una "overdose dopaminergica" alla base dei deficit esecutivi dei pazienti con malattia di Parkinson sotto trattamento farmacologico, ipotesi su cui dovranno concentrarsi futuri approfondimenti.

List of abbreviations

ACC	<i>Anterior cingulate cortex</i>
ANOVA	<i>Analysis of variance</i>
BG	<i>Basal ganglia</i>
BPT	<i>Brown Peterson Technique</i>
C	<i>Corresponding trial</i>
CE	<i>Central executive</i>
CNA	<i>Cognitive neuroscience of ageing</i>
CPA	<i>Cognitive psychology of ageing</i>
DA	<i>Dopamine</i>
df	<i>Degree of freedom</i>
DRT	<i>Dopamine replacement therapy</i>
EEG	<i>Electroencephalogram</i>
EF	<i>Executive functions</i>
ENB2	<i>Esame Neuropsicologico Breve 2</i>
ERPs	<i>Event related potentials</i>
FAB	<i>Frontal Assessment battery</i>
FLH	<i>Frontal lobe hypothesis</i>
FRN	<i>Feedback related negativity</i>
ICA	<i>Independent component analysis</i>
IGT	<i>Iowa gambling task</i>
KS	<i>Kolmogorov-Smirnov test</i>
MMSE	<i>Mini Mental State Examination</i>
ms	<i>Millisecond</i>
NC	<i>Non-corresponding trial</i>
η_p^2	<i>Partial eta square</i>
ns	<i>Non-significant</i>
PD	<i>Parkinson's disease</i>

PFC	<i>Prefrontal cortex</i>
rANOVA	<i>Repeated measure analysis of variance</i>
RT	<i>Reaction times</i>
SAS	<i>Supervisory attentional system</i>
sd	<i>Standard deviation</i>
TMT	<i>Trial making test</i>
UPDRS	<i>Unified Parkinson's Disease Rating Scale</i>
WM	<i>Working memory</i>
χ^2	<i>Chi squared test</i>

CHAPTER I

EXECUTIVE FUNCTIONS

“Human cognition is forward-looking, proactive rather than reactive. It is driven by hopes, plans, goals, ambitions, and dreams, all of which pertain to the future and not to the past. These cognitive powers depend on the frontal lobes and evolve with them. The frontal lobes endow the organism with the ability to create neural models as a prerequisite for making things happen, model of something that, as of yet, does not exist but which you want to bring into existence”.

(Goldberg & Bougakov, 2007)

1.1 Definition of executive functions

Despite the frequency with which it is mentioned in the neuropsychological literature, the concept of executive functions (EF) is linked to several problems, concerning definition, conceptualization and measurement. The reason of that is not the newness of this concept, because the notion of EF arose in the 1840s when scientists tried to understand the functions of the prefrontal cortex (PFC) (Luria, 1966; Harlow, 1868-1848). For this reason EF initially were generally defined as what the prefrontal lobes do (Pribram, 1976-1973), but of course this definition is insufficient. Research efforts, aimed to explore the different aspects of this complex concept, have often yielded contradictory findings, resulting in a lack of clarity and in the presence of controversies regarding the true nature of EF (Jurado & Rosselli, 2007). A clear definition of EF would be necessary to determine which human mental functions can be considered executive in nature and which one cannot be so classified (Barkeley, 2012).

Unfortunately, the concept of EF is actually expressed by different definitions (table 1), and there is neither a consensus definition nor an explicit operational definition of EF. Trying to summarize most points of view, it is possible to affirm that problem-solving, working memory, planning, sustained attention, inhibitory control, feedback processing, multitasking and cognitive flexibility are considered the “cool” components of EF.

At the same time, in EF construct are also included “hot” components, which are cognitive processes that involve more emotional arousal and are represented by the capacity to deal with novelty, decision-making, social and emotional behaviour regulation (Zelazo & Cunningham, 2007).

Currently, it is possible to consider EF as an “umbrella term” in which both cold and hot components are considered as high-level cognitive functions, which are involved in the control and in the regulation of lower-level cognitive and behavioural processes (Chan et al., 2008; Alvarez & Emory, 2006). Unfortunately, the lack of single agreed upon definition of EF is linked to other important open questions concerning EF: How do EF work? How are EF to be assessed? (Barkley, 2012). The aim of this chapter is to propose an overview of these critical issues about EF. To explain how EF work, principal cognitive and neuroanatomical models will be reviewed; moreover, a description of the principal methods for EF assessment will be provided.

TABLE 1.1 Sampling of definition of EF (adapted from Barkley, 2012).

AUTHOR/S	DEFINITION
Luria, 1976	... Executive processes are essential for the synthesis of external stimuli, formation of goals and strategies, preparation for action, and verification that plans and actions have been implemented appropriately.
Norman & Shallice, 1986	The umbrella concept of “executive control” encompasses those cognitive functions involved in the selection, scheduling and coordination of the computational processes responsible for perception, memory and action.
Stuss & Benson, 1986	Executive functions is a generic term that refers to a variety of different capacities that enable purposeful, goal-directed behaviour, including behavioural regulation, working memory, planning and organizational skills, and self-monitoring.
Baddeley, 1986	The term executive functioning generally refers to the mechanisms by which performance is optimized in situations requiring the operation of a number of cognitive processes.
Lezak, 1995	The executive functions consist of those capacities that enable a person to engage successfully in independent, purposive self-serving behaviour.
Burgess, 1997	[Executive functions are] a range of poorly defined processes which are putatively involved in activities such as “problem solving”... “planning”... “initiation” of activity, “cognitive estimation” and “prospective memory”.
Anderson, 2002	Executive functions are responsible for coordinating the activities involved in goal completion such as anticipation, goal selection, planning, initiation of activity, self-regulation, deployment of attention and utilization of feedback.

1.2 Theories and models of executive functions

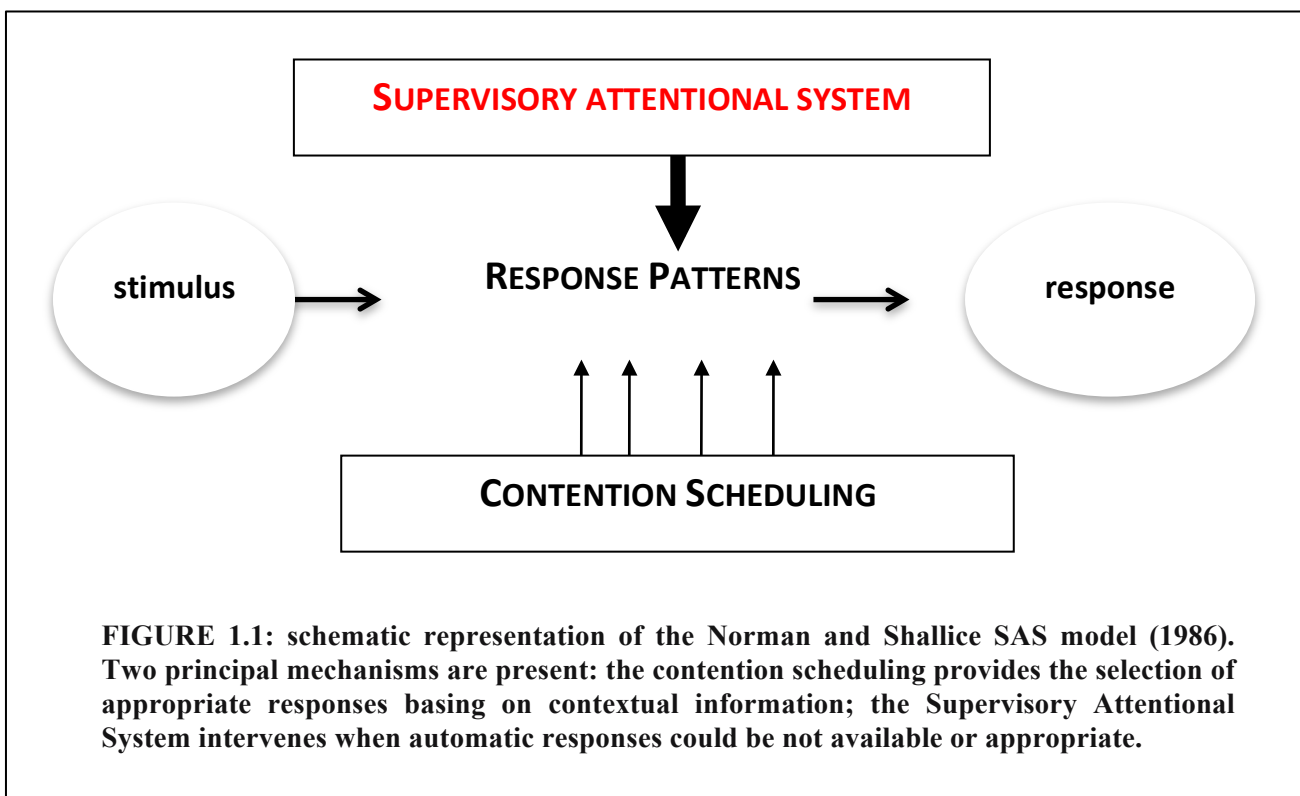
Alexander Luria was one of the first scientists who wrote extensively about EF. His EF theory was developed documenting the behaviour of patients with frontal lobe damage. For this reason, Luria's functional analysis referred to what EF are and do in terms of cognitive and behavioral outcomes of a frontal damage. Luria (1976-1966) postulated the existence of three functional brain units. The first is a subcortical unit, mainly located in the brain stem, and it is responsible of arousal and consciousness. The second unit, which refers to the temporal, parietal and occipital lobes, is responsible for encoding, processing and storage of sensory information. Finally, the third functional unit consists of the frontal lobes, which is responsible of programming, regulation and verification of goal-directed behaviour. With this model Luria (1976-1966) proposed that the prefrontal cortex (PFC), included in the third unit, is superimposed on all other cortical areas, and performs a role of supervision and regulation of mental activity and behaviour. According to this model, damage to the frontal lobe, and in particular the PFC, is expected to, causing several cognitive and behavioural disorders linked to an inefficient regulation of behavioural outcomes.

After Luria, different theories and models accounted EF using the concept of a central control system. These models, which agree about complexity and importance of EF to human adaptive behaviour, proposed different conceptualizations regarding what mental processes actually constitute EF, the presence of possible subcomponents, and which are the variables that measure them. In the effort to develop a coherent EF model, two main branches of theories were followed: models in which one single underlying ability explains all the components of EF, developed by unitary theories of EF, and models in which EF constitute related but distinct processes, inspired by multiple processes theories of EF (Jurado & Rosselli, 2007).

The two main representative models inspired to unitary theories are the Norman and Shallice (1986) and the Baddeley and Hitch's (1974) models (see also Baddeley, 2000-1986). The first (Norman & Shallice, 1986) is based on the existence of two principal systems, responsible of programming, regulating and verifying of human actions (figure 1.1). The first system, called Contention Scheduling, has the control of routine and overlearned actions and provides the selection of appropriate responses basing on contextual information. The second system, on the other hand, occurs in non-routine situations, where automatic responses could be not available or appropriate.

This second system is called Supervisory Attentional System (SAS) and represents the higher control mechanism necessary for the correct behavioural regulation.

Similarly to Norman and Shallice's model (1986), also in the Baddeley and Hitch's (1974) model was hypothesized the presence of a higher control mechanism, even if the authors' goal was to clarify the role of working memory within EF. In fact, together with a Central Executive (CE), responsible for the control and regulation of cognitive processes, Baddeley and Hitch's model (1974) involves three subsidiary systems: a visuo-spatial sketchpad for the manipulation of visual information; a phonological loop, for the manipulation of speech-based information; finally an episodic buffer, which links information across domains to form integrated episodic representations of visual, spatial, and verbal information. Comparing the two models, both SAS (Norman & Shallice, 1986) and CE (Baddeley, 2000; Baddeley and Hitch, 1974) models represent central and supervisory systems that preside over cognitive processes.



In addition to the two main theories explained above, other unitary theories of EF could be found in the literature. The Duncan's goal neglect theory (Duncan, 1986; see also Duncan et al., 2000; Duncan & Owen, 2000; Duncan, 1995) can be considered another unitary theory of EF.

Analysing clinical evidences, Duncan and colleagues suggested that the principal deficit of patients with frontal lobe damage concerned the loss of control of action and its desired results. On the basis of these evidences, Duncan proposed a model of EF emphasizing the role of goals in the behavioural regulation: goals impose a structure on the behaviour, by controlling the activation or the inhibition of actions.

Duncan proposed that the common mechanism that underlies EF is the behavioural organization depending on the goals achievement. Following this model, behaviour would be under the control of particular set of goals, which elicit the relevant actions from a large potential store of behaviours. These goals are formulated, stored and checked by a subjective order, to behave optimally and properly in response to environmental or internal demands (Chan et al., 2008). The goal achievement is related to the function of the frontal cortex and in patients with frontal lobe damage, the typical structure of goal directed behaviour is disrupted. Patients with frontal lobe damage are able to remember the intended goals, however they show a disorganized behaviour, failing to achieve the intended goals. Duncan (1986) referred to the executive dysfunction of these patients with the expression “goal-neglect”.

In contrast to the described unitary views, different EF theories were proposed, excluding the existence of an underling unique system and stressing a multiple nature of EF. These multiple processes theories permitted the elaboration of different EF models, developed with the aim to add details and levels to the unitary models.

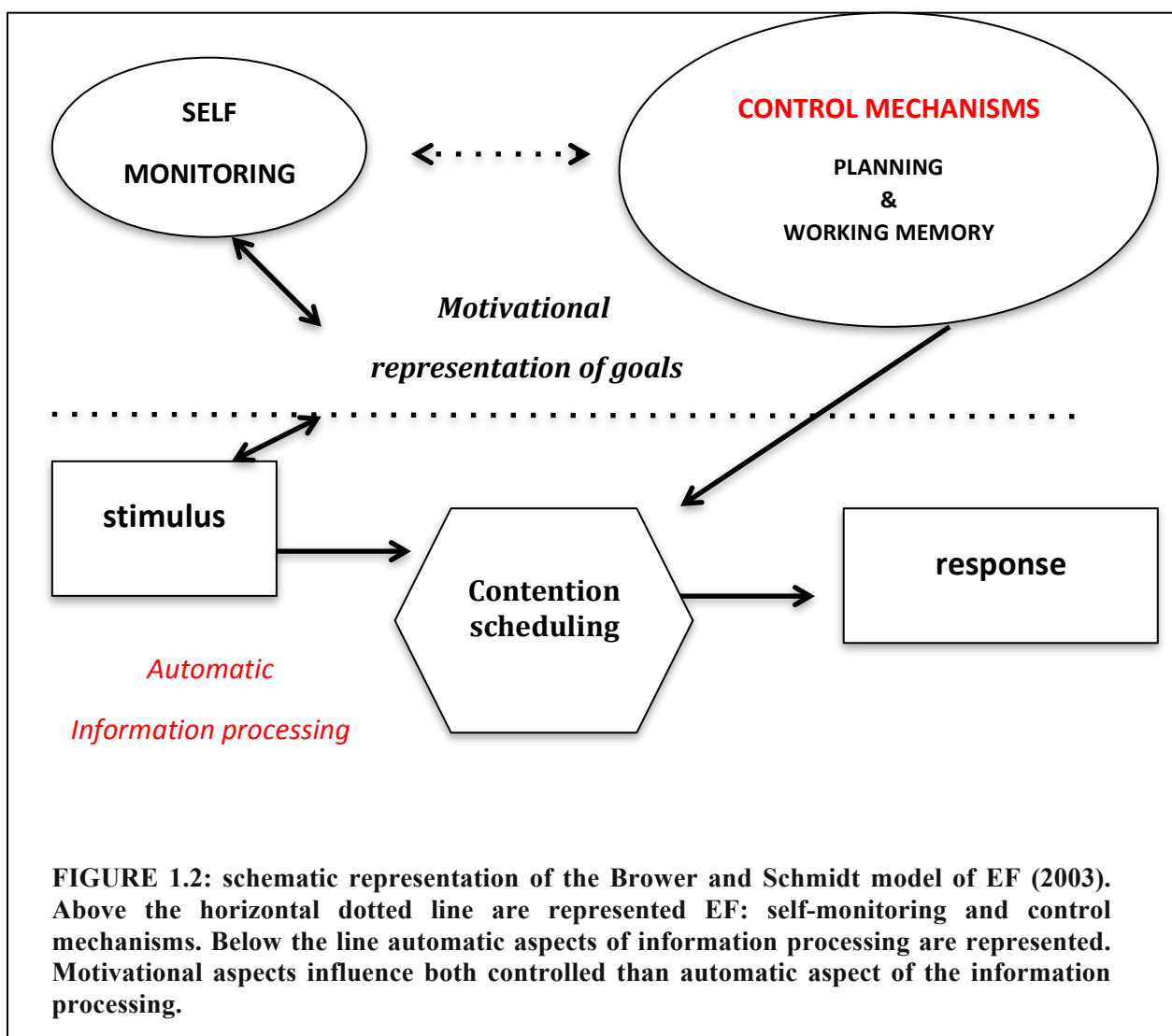
An example of multiple processes model is the Fuster’s (1997) cross-temporal synthesis model.

As Duncan, Fuster (1997) focused on the goal achievement capacity, defined as cross-temporal synthesis. Fuster’s model excluded the concept of a central executive control system and represented EF as the integration of multiple components. Fuster sustained that goal directed behaviour is realized by the representation of events, responses and goals. These three representations arise from three specific EF components: working memory, planning and interference control. According to Fuster (1997), these three EF components are fundamental for the “cross-temporal organization of behaviour”. Deficits in any of the three components can result in a deficient temporal integration of behaviour, and give rise to distinct disorders of EF.

Few years later, Stuss and Alexander (2000) elaborated a different multiple processes model.

Offering a different interpretation of the SAS model (Norman & Shallice, 1986), Stuss and Alexander (2000) proposed the existence of three levels of behavioural monitoring, which developed progressively in humans. The first level comprises the automatic execution of overlearned routine activities. This level is suggested to reflect the function of subcortical systems (Slattery et al. 2001). The second level includes the information-processing act to organize a goal-directed behaviour; this level reflects the function of a controlled mechanism with supervisory function. The third and highest level is represented by the awareness, of both oneself and the environment. Adding this third level, Stuss and Alexander (2000) integrated the SAS model (Norman & Shallice, 1986) with an higher level of control, going beyond the distinction between controlled and automatic processes, indicted to be insufficient for explaining EF.

A final example of a multiple processes theory is provided in figure 1.2, which describes the model of Brower and Schmidt (2003).



Even this model could be considered as a supplement to the Norman and Shallice's model (1986). Brower and Schmidt (2003), in fact, confirmed the presence of both controlled and automatic processes, adding however more details. Authors translated the concept of contention scheduling talking about the automatic information processing and hypothesized the existence of a more complex control mechanism. In the model of Brower and Schmidt (2003), planning and working memory abilities are required in condition of discrepancy between actual and required goal attainment. These two abilities work together as a control mechanism that intervenes when automatic processing is not sufficient. Respect to the SAS model (Norman & Shallice, 1986), Brower and Schmidt (2003) introduced the concepts of motivation and awareness to explain the collaboration between controlled and automatic information processing. In detail, automatic information processing interacts with a motivational representation of goals. This motivational representation would influence also the controlled processing, interacting with a self-monitoring process, critical for the activation of the controlled mechanism, and then for the appropriate behavioural management (Brower & Schmidt, 2003).

In summary, both unitary and multiple processes models can be classified as hierarchical models that, interpreting EF as the higher level of cognition, respectively identifying one or more mechanisms to represent this level, necessary for the appropriate cognitive and behavioural regulation.

The clinical observation of double dissociations, together with the increasing results of functional neuroimaging studies, sustain a multi-component view of EF, in which may coexist the presence of clearly distinguishable domains that, at the same time, share some underlying commonality (Salthouse, 2005-1996; Fisk & Sharp, 2004; Miyake et al., 2000). This multi-component view is also the emerging idea in the debate about the neural basis of EF: as will be explained in the next paragraph, what is emerging from functional and clinical evidences is the idea that different EF are not mediated exclusively by the frontal areas, but depend on different brain regions as well (Boelen, 2011).

1.3 Neural basis of executive functions

The earlier studies on neural basis of EF are linked to the observation of patients with frontal lobe damage, who often showed cognitive and behavioural abnormalities attributable to an EF deficit. In a first attempt to find a specific correspondence between neural substrate and cognitive functions, different components of EF were associated with three principal regions of the PFC (Sbordone, 2000; Cummings, 1995; Stuss & Benson, 1984). The dorsolateral PFC was related to planning, problem solving, working memory and mental flexibility, while the ventromedial and the orbital sections of the PFC were associated inhibition capacity, drive and initiative, and the regulation of social behaviour (Grossi & Trojano, 2005). Despite the fact that this distinction is based on clinical and functional evidences and still represents the principal functional framework of EF, it is obviously a schematic model of anatomical-functional correspondence.

Given the complexity of the argument, even in this case there is no clear agreement about neural basis of EF: as consequence of different evidences, there remains an on-going debate regarding how EF are regulated by the frontal cortex (Alvarez & Emory, 2006; Welsh, 2002; Miyake et al., 2000). As defined by Stuss and Knight (2013) the frontal cortex is "... one of the latest structure of the brain to evolve, uniquely endowed with the capacity to pre-adapt the human being to her environment, and connected practically to every other structure of the brain". This assumption highlights the importance to consider the connections between frontal cortex and other brain structures, in the study of neural basis of EF. In fact, together with evidences of specific associations between EF and different regions of the frontal lobes (Stuss et al. 2002; Koechlin et al. 2000; Stuss & Alexander 2000), is now accepted that EF are as well distributed over a wide cerebral network, which includes subcortical structures and thalamic pathways (Jurado & Rosselli, 2007; see also Monchi et al. 2006; Kassubek et al. 2005; Lewis et al. 2004).

This shared idea of a dynamic and flexible network that supports EF (Elliott, 2003) is sustained by several imaging and lesion studies. In a meta-analytic review, Alvarez and Emory (2006) provided a critical analysis of lesion and neuroimaging studies using EF measures. In detail, authors examined the validity of EF construct in terms of its relation to activity and damages to the frontal lobes. Alvarez and Emory (2006) found inconsistent results that did not support a one-to-one relationship between EF and frontal lobe activity: many functional neuroimaging studies, which explored neural

basis of EF using validated measures, demonstrated that the performance at these tests is often related to a distributed neural activation, of frontal and non-frontal brain regions. For example, particular attention has received the exploration of subcortical and thalamic pathways that originates in the PFC (Royall et al. 2002; Baddeley, 1998). In detail, connections between PFC and subcortical structures as the caudate, striatum and the nucleus accumbens, are now considered as crucial for the EF. The mentioned distinction between the functional roles of dorsolateral, ventromedial and orbitofrontal cortex is in fact currently translated in the study of the dorsolateral, ventromedial and orbitofrontal pathways functions (see figure 1.3).

Exploring the involvement of these pathways instead of PFC regions, several evidence promoted a more complete view of EF neural bases.

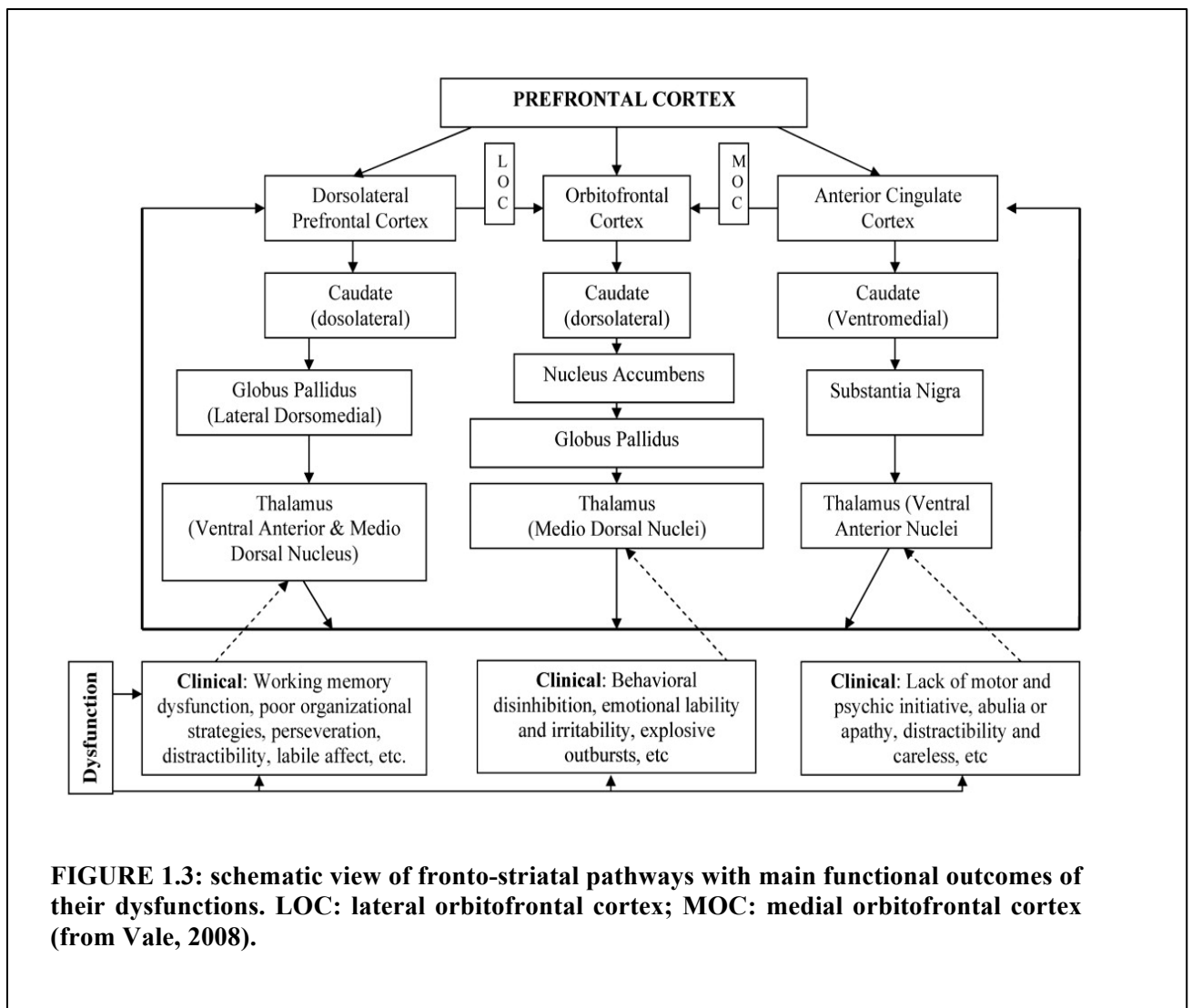


FIGURE 1.3: schematic view of fronto-striatal pathways with main functional outcomes of their dysfunctions. LOC: lateral orbitofrontal cortex; MOC: medial orbitofrontal cortex (from Vale, 2008).

Mental flexibility, set shifting and planning, together with working memory, reasoning, problem-solving and abstract thinking, are now related to the projections of the dorsolateral PFC to the dorsolateral head of the caudate nucleus (Malloy & Richardson, 2001; Duke & Kaszniak, 2000; Grafman & Litvan, 1999; Cummings, 1993; Jonides et al., 1993; Ettliger et al., 1975; Milner, 1971). Inhibition capacity and emotional regulation are now considered as linked to the orbitofrontal pathway, which involves the dorsolateral caudate nucleus and the nucleus accumbens (Cummings, 1995; Blumer & Benson, 1975). Finally, motivation, initiative and the regulation of social behaviour are now related to the ventromedial circuit, which involves the anterior cingulate cortex, connected to the ventromedial caudate nucleus (Sbordone, 2000).

Taken together, even if these evidences demonstrated that PFC has a main role in EF, they also highlight that different brain regions are involved in EF. Being the higher-level of cognitive processing, it is likely that EF requires participation and coordination of activities among different brain areas. Therefore, it is possible to consider EF as a “macro-construct”, in which different high order abilities refer to the functioning of PFC and brain regions to it connected.

1.4 Evaluation of executive functions

After defining EF on behavioural and anatomical levels, the question arises how these functions could be assessed. The on-going controversy regarding the formal definition of EF makes the assessment of these functions a delicate matter. In absence of an operational definition of EF, the question is about what method is qualified as a measure of EF and what is not. Neuropsychology answered this question using psychometric tests, built on the basis of their sensitivity to prefrontal damages. Several instruments, described as “frontal” tests, were developed to measure EF and are widely used in research and clinical practice (see table 1.2). However, there is an on-going debate on approaches to measuring EF and no gold standard for the EF assessment has been agreed upon. Despite the clinical utility of the most common EF tests, three main methodological problems motivate this debate.

Firstly, most of the conventional EF tests may be limited by their own test-retest reliability.

Theoretically, only novel task can assess EF: for this reason, the test-retest reliability of an EF test is usually relatively low (Rabbitt, 1997). Secondly, a lack of ecological validity characterizes some of these tests: different findings reported a low correlation between the performance at these tests and the real life activity functioning of frontal patients (for reviews see Barkeley, 2012; Jurado & Rosselli, 2007). Finally, there is the problem of “task impurity” (Burgess, 1997), caused by the nature of EF construct. In fact, the execution of a task, believed to measure EF, can in reality trigger non-executive lower level processes, which are unrelated but necessities to the execution of the task (Hughes & Graham 2002). Taken together, all these methodological problems arise from the lack of a shared operational definition. Validity and task specificity of a test are in fact difficult to determine when the construct to measure is ill defined.

In conclusion, the evaluation EF is a thorny matter. Until new methods will be developed, the study of EF can rely on tests that have been historically purported as measuring the functions of the frontal lobe (Jurado & Rosselli, 2007). However, all the methodological limits of these tests justify the development of new tasks and new procedures for the study of EF, of which an attempt will be presented in this thesis.

TABLE 1.2 Common EF tests used in clinical and research practice.

Test	EF components evaluated
Stroop test (Stroop, 1935; Golden, 1978)	Inhibitory control
Trial Making Test (AITB, 1944; Reitan, 1955-1992)	Set- switching; Inhibitory control
Simon task (Simon, 1969)	Cognitive control
Tower of London (Shallice, 1982)	Planning
Wisconsin card sorting test (WCST; Heiton et al., 1993; modified version Nelson, 1976)	Set shifting; Set maintenance; Inhibitory control; Rule detection
Phonemic fluency Test (Benton and Hamsher; 1989)	Verbal production; Response generation; Inhibitory control
Semantic fluency Test (Goodglass & Kaplan, 1972)	Verbal production; Mental flexibility; Inhibitory control
Iowa Gambling task (Bechara et a., 1994)	Feedback based learning; Decision making
Sustained attention to response task (SART; Robertson et al., 1997)	Sustained attention; Inhibitory control
N-Back task (Callicot et al., 1998)	Working memory; Monitoring
Frontal Assessment Battery (FAB; Dubois et al., 2000)	Abstract thinking; mental flexibility; Inhibitory control; Environmental independence
Behavioural Assessment of Dysexecutive Syndrome (BADS; Wilson et al., 1996)	Planning; Organising; Initiating; Monitoring; Problem solving; Adapting behaviour

CHAPTER II

AGEING AND EXECUTIVE FUNCTIONS

2.1 Executive functions in cognitive psychology of ageing

The understanding of age-related changes in cognitive processes, i.e. the object of the cognitive psychology of ageing (CPA), is increased over the last 50 years. Precisely, what is increased concerns both theories and methods for the study of cognitive ageing. Understanding of age-related changes in cognition is challenging and uneasy for several reasons. Firstly because behavioural research on ageing has mapped contrasting patterns of both decline and stability in cognition across the adult lifespan (Hedden & Gabrieli, 2004); secondly because cognitive effects of old age vary in frequency, direction, and extent (Band et al. 2002). As pretty much in every scientific field, what research does is to try to increase the knowledge, building, improving and integrating theories and methods. The proof of this growing process is the presence of many, older and newer, models and theories about cognitive ageing, that were developed with the principal aim to identify explanations that are coherent with the empiric results.

Several CPA models and theories have been developed. First models have tried to define the age-related changes as qualitative or quantitative, or categorized these changes as impairments in low or high levels of cognitive processing (Band et al., 2002); more recent approaches focus on a different kind of distinction. The prevalent dichotomy in modern CPA theories is between specific or general impairments. The current debate is in fact between theories that account for the existence of specific age-related cognitive impairments and theories that attribute the effect of ageing on cognition to limited and more general cognitive mechanisms (for a review see Hertzog, 2008). The general models that are supported by meta-analyses of data across different task domains, try to identify a single factor that may explain the variability, while the specific models focus on a more circumscribed and domain specific view of cognitive ageing, demonstrating task-specific inconsistent changes.

The most representative general models on cognitive ageing are: the *processing resource* theory (Hultsch, 1998; Salthouse, 1991), the *self-initiated processing* theory (Craig & Byrd, 1982) and the *inhibitory loss* theory (Hasher & Zacks, 1988).

While the first theory was initially focused on the *speed of information processing* theory (Salthouse, 1996; Cerella, 1990) and later evolved addressing a cognitive resources decline as unifying metaphor of cognitive ageing, the other two theories are closer to the concept of executive functions (EF) or executive control. In fact, Craik & Byrd (1982) proposes an age-related deficiency in on-line processing resources and attentional capacity, suggesting that older adults are lacking in the ability to engage self-initiated processes, which require conscious effort and are typically considered EF. At the same time, Hasher and Zacks (1988) emphasize the age-related changes in focussing on target information, and in inhibiting attention to irrelevant material; They sustained that the inhibitory control represents a fundamental variable to understand cognitive ageing (Hasher & Zacks, 1988).

Specific models, which do not have the aim to find a unifying metaphor, are represented by single domain theories. These models report and sustain age-related changes in particular classes of cognitive functions such as memory (Schacter et al., 2012; Light, 2000-1991; Jacoby, 1999; Kensinger & Schacter, 1999) or EF (Butler et al., 2004; Mayr et al., 2001; Johnson & Raye, 2000; Hasher & Zacks, 1988).

As this short review of the current theoretical status suggests, the concept of EF is a recurring theme in CPA. EF have been invoked more than once to explain ageing-related cognitive changes, as a specific target of deficit (Butler et al., 2004; Mayr et al., 2001; Johnson & Raye, 2000) or as a general underlying mechanism whose dysfunction can justify specific deficits in other domains (Salthouse, 1996; Cerella, 1990; Hasher & Zacks, 1988; Craik & Byrd, 1982). However, these theories have tried to give an explanation of cognitive ageing without any link to brain ageing. In this regard, cognitive neuroscience of ageing is aiming to specifically link cognitive ageing to brain ageing.

2.2 Executive functions in cognitive neuroscience of ageing

Until recently, the cognitive and neural mechanisms of age-related changes in cognition were studied independently of each other (Cabeza et al., 2005). Research on CPA has the aim to investigate age related changes on cognition and behaviour, while neuroscience of ageing investigates age related modifications on the anatomy and physiology of the brain.

The emergence of a relatively new discipline, cognitive neuroscience of ageing (CNA), represents the need to link the effects of ageing on cognition with the effects of ageing on the brain. Although the link between cognitive and brain impairments in ageing seems quite obvious, the nature of these brain-behaviour relationships is still largely unknown (Cabeza et al., 2005). In fact, mapping cognitive operations onto neural circuitry is a challenging task, not only because cognitive theories can lack precision or can be conflicting, but also for several biological and methodological limits (for a review see Hedden & Gabrieli, 2004). First of all, from a biological point of view ageing is strongly associated with risk for numerous pathologies: even when working with highly selected healthy older adults, research indicates that normal ageing is associated with changes in the neural basis of cognition (Hedden & Gabrieli, 2004). Secondly there are also two methodological factors. The first one is the use of correlational analysis. This kind of analysis is used because age cannot be experimentally manipulated, but at the same times it leads to a lack of causal relations in the results. The second is the employment of cross-sectional comparisons between age groups, method justified by the cost and the complexity of longitudinal research, but that provides valid but less reliable results. Finally, the combination of these limits: many brain and mental changes can occur in parallel during ageing, and the most common methodological approaches make it difficult to establish reliable relations.

In spite of these challenges, advances in neuroimaging techniques have helped to deal with some of these limits and they have allowed the elaboration of different theories and subsequent models (Cabeza et al., 2005). Specifically, it is possible to distinguish two classes of models: models that refer to age related changes in hemispheric lateralization, and models that focus on an age related anterior-posterior asymmetry. Two main models represent the first class. The *right hemi-ageing model*, which states that the right hemisphere is more sensitive to the harmful effects of ageing than left hemisphere (Dolcos et al., 2002). This model is primarily based on behavioural rather than neurobiological data and this lack of evidences stimulated the elaboration and the advancing of a second model, known as HAROLD (*Hemisphere Asymmetry Reduction in Older Adults*; Cabeza, 2002). HAROLD model states that, under similar conditions, the activity of the prefrontal cortex (PFC) tends to be less lateralized in older than in younger adults (Cabeza, 2002): elderly are more likely to rely on both hemispheres in condition in which unilateral recruitment is sufficient in young adults (Daselaar & Cabeza, 2005).

Describing the HAROLD model, Cabeza (2002) explained the smaller lateralization in older adults invoking a compensation mechanism. In fact, the cooperation between the two hemispheres is more advantageous than a within-hemisphere processing in situations of high task demand (Weissman & Banich, 2000; Brown & Jeeves, 1993; Banich & Belger, 1990). Following this explanation, older adults that experience higher task demands, respect to younger adults, would show a greater hemispheric collaboration and a smaller lateralization in the activity of the PFC. Findings in support of the HAROLD model (Cabeza, 2002) are numerous and have specially been reported in the domains of working memory, attention, and inhibitory control processes. Data supporting this theory refer on several experimental evidences (Daselaar et al., 2003; Rosen et al., 2002; Reuter-Lorenz et al., 2000; Rypma & D'Esposito, 2000).

In the second class of models, i.e. models that take into account age related anterior-posterior asymmetry, the *Frontal Lobe Hypothesis* (FLH) formulated by West (1996) represents a dominant view and probably one the most accredited theory. According to the FLH, cognitive processes supported by the PFC will manifest age-related decline at an earlier age and in greater magnitude, than cognitive processes supported by non-frontal regions (West, 2000; West, 1996). This theory states that, due to differential age related decline of neural tissue in the PFC, cognitive functions supported by these areas are more susceptible to age effects than functions that rely on posterior and subcortical areas (Band et al., 2002). There are many functional and structural neuroimaging studies that support this theory.

According to past and recent findings, ageing effects on the PFC consist in a decreasing of myelin (Albert, 1993), white matter degeneration (Raz et al., 2005; Guttmann et al., 1998), decreased neurotransmitter response (Fulop & Seres, 1994) and decreasing metabolic activity (Uylings et al., 2000; West, 1996; Salmon et al., 1991). Even if these data support the FLH theory, common critics to this model include the fact that it is supposed to be based on both weak and conflicting neuroimaging evidences (Band et al., 2002; Greenwood, 2000; Wickelgren, 1996) and on behavioural data based on measurements that may be sensitive to more dysfunctions than only that of the PFC (Band et al., 2002).

These criticisms are strictly linked to a main issue described in the previous chapter: the fact that defining frontal lobes functions and EF neural correlate is a really difficult task.

This complexity reflects on one hand the definition of the functions subjects to decline and, on the other hand, the functional meaning of brain changes. Ideally, to refine this hypothesis, that is still one of the most accredited, research should consider all the neural networks and the functional activity of the circuitries in which frontal regions are involved (Tisserand & Jolles, 2003). This is exactly what the current trend of research in CNA is aiming to do. In fact the new neuro-computational approaches suggest that “ageing related changes in the dynamical properties of cortical functions could be related not only to neuroanatomical degeneration, but also declines in neurochemical processes affecting pattern representation and information transfer within and between cortical regions” (Daselaar & Cabeza, 2005).

One of the most recent hypotheses in CNA suggests that cognitive ageing may be related to principal decline of dopaminergic modulation in both PFC and different subcortical regions (for a review see Bäckman et al., 2010-2006). Even if details regarding the involvement of neuro-modulation in cognitive ageing deficits remain to be investigated, this recent hypothesis is based on the integration of many evidence. Together with findings about the primary PFC involvement and about age-related decline of EF (Daselaar & Cabeza, 2005), several evidence sustain the presence of a deficient dopaminergic modulation in ageing. This last finding is important because of shared knowledge about the relation between dopamine (DA) and cognition. Recent researches, in fact, suggest that DA has not only a central role in motor functioning but is also critically implicated in higher-order cognitive abilities (Bäckman et al., 2006). Studies on clinical populations with severe alteration of DA system, such as Parkinson’s disease (PD) and Huntington’s disease (HD), indicated that patients showed deficits across multiple cognitive domains, including EF (Kudlicka et al., 2011; see also Brown & Marsden, 1990; Brandt & Butters, 1986). Furthermore animal study evidence have shown an association between the degeneration of dopaminergic pathways and deficits in memory (Simon et al., 1986), inhibition (Jones & Robbins, 1992), spatial attention (Boussaoud & Kermadi, 1997) and set-shifting (Robert et al., 1994). An important role in supporting this theory is played by pharmacological studies on humans and animals, which have found that the manipulation of DA transmission may be related to cognitive performance in working memory tasks (Kimberg & D’Esposito, 2003; Mattay et al. 2003; Mehta et al., 2000; Luciana et al. 1998-1992; Luciana & Collins, 1997) and in the speed of information processing (Ramaekers et al., 1999; Halliday et al., 1994).

Similar results were found in genetic research. It was demonstrated that performance enhancement in working memory task emerged after the inhibition of COMT (Kneavel et al., 2000, Gogos et al., 1998; Gasparini et al., 1997; Liljequist et al., 1997) an enzyme that inactivates extracellular DA especially in the PFC.

Given these consistent evidences, it is possible to confirm the existence of a relation between DA and cognition: this is an important assumption in the light of the numerous evidences about age-related losses of dopaminergic functioning. Specifically, there is extensive evidence for a main age-related loss in various biochemical markers of the nigrostriatal DA system, both post-synaptic markers as DA receptors (Ichise et al., 1998; Wang et al., 1998; Antonini et al., 1993; Suhara et al., 1991; Rinne et al., 1990; Cortes et al., 1989; Seeman et al., 1987; Severson et al., 1982;) and pre-synaptic as DA transporters (Ma et al., 1999; Rinne et al., 1998; Bannon & Whitty, 1997; Van Dyck et al., 1995; Bannon et al., 1992; Allard & Marcusson, 1989).

Without going into detail of this specific literature, the main point to highlight is that these two kinds of finding have a complementary role in the study of cognitive ageing. The decline of both DA markers and cognitive efficiency with advancing age, together with the findings about the role of DA on cognition, have stimulated the examination of a relationship between age-related changes in DA functioning and age-related changes in cognition (Daselaar & Cabeza, 2005). To explore this connection, a modelling approach is going to be adopted. This approach is integrating the empirical evidences about the role of dopamine in cognitive functioning into neuro-computational models. The work of Li and colleagues (2001) is particularly relevant as, by modifying a previous model (Servan-Schreiber et al. 1998), they elaborated a model in order to link age-related cognitive deficits to deficient dopaminergic modulation. The model accounts for an inverted U-shaped dose–performance function (see figure 2.1) by demonstrating that a normal cognitive performance is related to optimal DA levels, while extremely low or high DA levels result in poorer cognitive performance (Li & Sikström, 2002; Li et al., 2001). As recently suggested by Vaillancourt and colleagues (2013), the interpretation of this interesting model (Li et al., 2001) should be integrated taking into account many other factors that could contribute to this inverted U relation, such as the regional striatal topography of nigrostriatal denervation, the individual genetic factors that can affect dopaminergic functions itself, determining the relative baseline position on this inverted-U curve.

However, from this model it is possible to extract an important assumption: while a normal cognitive performance is associated to an optimal dopamine level, a poor cognitive functioning is related to irregular dopamine levels, both lower and higher than normal, i.e. a dopamine dysregulation.

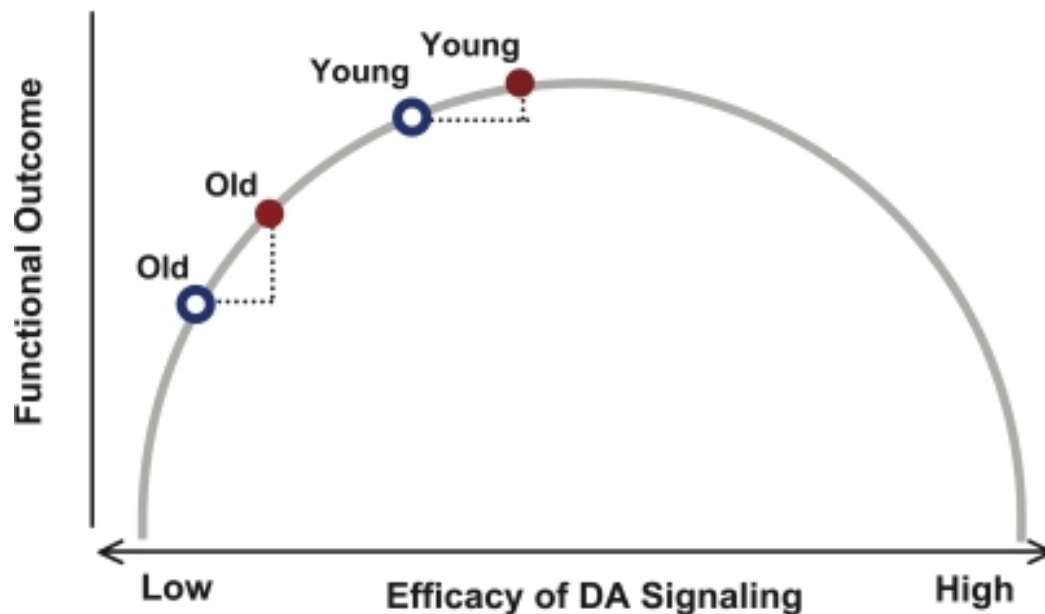


FIGURE 2.1: inverted U-shaped function linking the efficacy of DA signalling in early and late adulthood cognitive performance. Baseline position is determined by different factors, as genotype. (Adapted from Nagel et al., 2008)

Taken together, these findings suggest that patterns of age brain changes, such as the declines of dopaminergic modulation in the PFC and in linked subcortical regions, could be associated with age related deficits in EF. However this is a recent point of view and many specific mechanisms of neuro-modulation in cognitive ageing deficits remain to be investigated.

2.3 Executive functions in ageing: current view

As mentioned previously, the elaboration of cognitive ageing theories were always based on the empirical observation. Firstly inspired by cognitive theories, then by neurocognitive theories, every model represents the effort to explain the behavioural data collected, interpreting cognitive changes related to ageing.

With this aim both the FLH (West, 1996) first, and the neuromodulation hypothesis in recent times, have tried to explain cognitive ageing phenomenon focusing on the neural basis of consistent behavioural data. In fact, both these perspectives have focused on evidence of an EF involvement in the manifestation of age-related cognitive deficits. They are based on the assumption that the disruptions of the executive control might affect performance in a wide variety of cognitive tasks (Salthouse et al., 2003) and, integrating behavioural and neuroimaging data, suggested coherent and convincing models.

However, the complexity of the issues involved in this theoretical challenge brings inevitably to a prickly situation. West himself proposed a refinement of FLH, following the identification of differential age-related decline within the PFC, and suggesting the exploration of differential ageing effects on the various cognitive processes supported by the PFC (West, 2000). Following this aim, current research directions are oriented to the identification of age-related changes in executive sub-processes. As interestingly summarized by Verhaeghen (2011), the actual question is not, “Are there age-related differences in executive control?” but it became “Are there unique (i.e. specific) age-related deficits in executive control?”. To answer this question, research efforts are now directed to explore age-related changes in specific EF subcomponents.

Even in this case, discrepant results are expected, as natural consequence of the complexity of EF concept. However, new investigations in this field are necessary to fill the lack of consistent results on the pattern of ageing effect on EF (for a review see Verhaeghen, 2011).

Therefore the main goal of the three studies reported in this thesis is to explore age differences in specific EF subcomponents to better understand age-related cognitive changes. Specifically, we chose to explore EF as working memory, reward based learning and outcome monitoring, abilities that, according to the literature, are also associated with the dopaminergic activity in the PFC (Bäckman & Farde, 2005; see also Hämmerer & Eppinger, 2012; Bäckman et al., 2010-2006).

CHAPTER III

PARKINSON'S DISEASE AND EXECUTIVE FUNCTIONS

Parkinsonism is a syndrome that is clinically defined by the presence of motor features, particularly tremor at rest, rigidity, bradykinesia, and gait and postural abnormalities. The most common form of Parkinsonism is the idiopathic variety known as Parkinson's disease (PD). PD is now the second most common neurodegenerative disorder after Alzheimer's disease, with a reported overall incidence rates between 9 and 22 per 100,000 person-years in Europe (Wirdefeldt et al., 2011).

PD was firstly recognised as a unique clinical syndrome by James Parkinson in his work: 'Essay on the Shaking Palsy' (1817). In this essay Parkinson stressed the crucial role of motor impairments in the defining pathology of PD. This first description has influenced following studies and made PD traditionally considered a motor system disorder. Thank to several research and clinical reports, PD is now considered to be a much more complex syndrome involving motor as well as non-motor systems (Jankovic, 2007). In this chapter, after a brief explanation of neural pathophysiology of PD, cognitive symptomatology developed by PD patients will be described, focusing in detail on the executive dysfunctions.

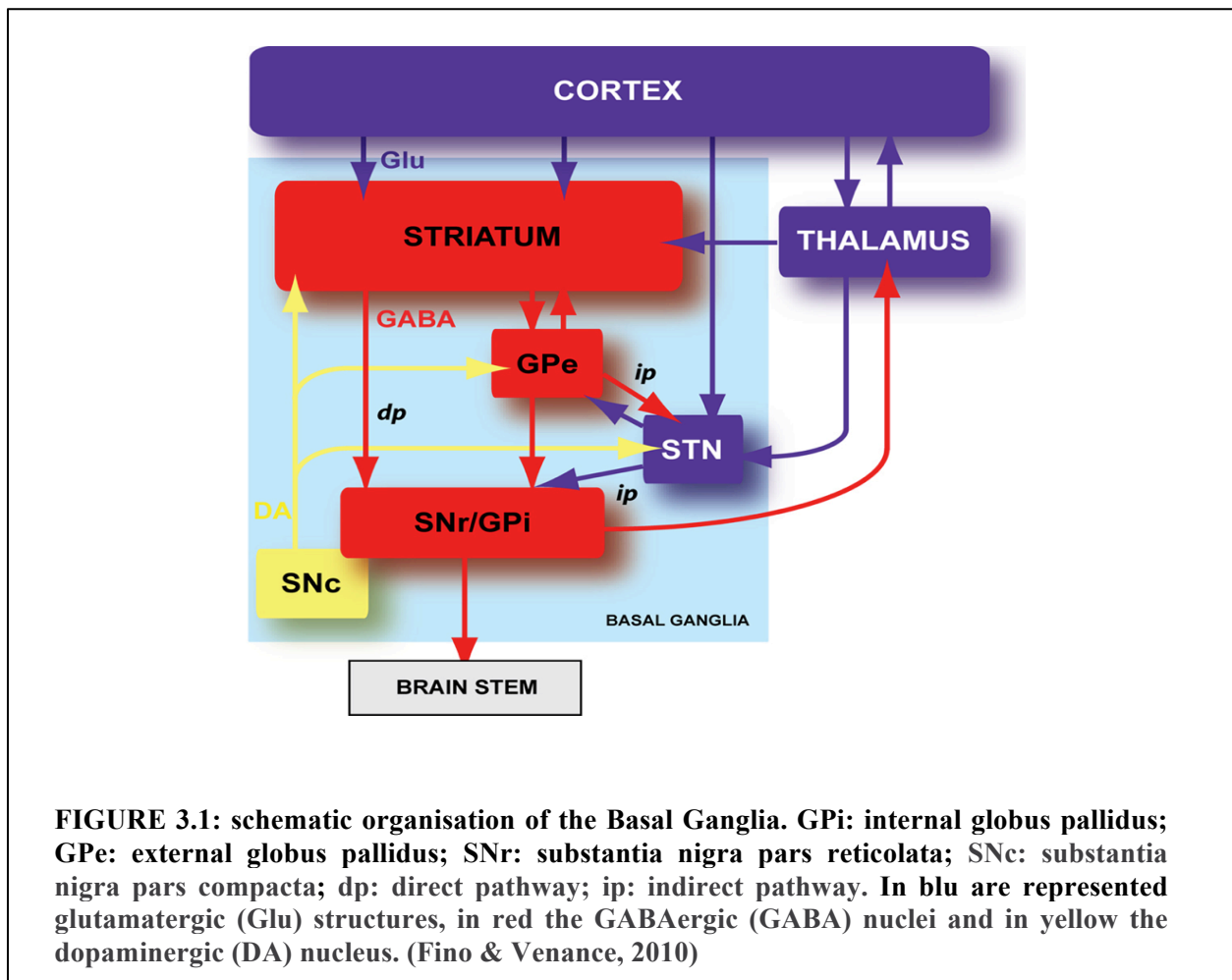
3.1 Neural pathophysiology of Parkinson's disease

The main pathologic feature of PD, and essential for its diagnosis, is the loss of dopaminergic neurons of the substantia nigra pars compacta, one of the structures of the basal ganglia (BG). The BG is set of interconnected subcortical nuclei, which represent a key part of the extrapyramidal motor system and that are also involved in motivation and cognitive functions.

BG activity is the result of a complex circuit, in which the primary input nucleus is the striatum, tha includes both putamen and caudate nucleus. The striatum, in fact, receives excitatory afferents from the cortex and thalamus, as well as dense innervation from midbrain DA neurons, and represents a major site of synaptic plasticity in the BG (Gerdeman et al., 2003; Bolam et al., 2000; Gerfen, 2000; Wilson, 1998).

BG circuit is based on the segregation of information processing into a direct and an indirect pathway (figure 3.1), which act in opposing ways to control movement (Kreitzer & Malenka, 2008). These two pathways represent two parallel cortex-BG-thalamus-cortex loops, which diverge within the striatum and are differentially modulated by DA.

The net effect of direct-pathway activity is the facilitation of movement, while the net effect of indirect-pathway activity is the inhibition of movement.



In PD the loss of DA neurons in the substantia nigra, that could reach 60% even in mildly affected PD patients, accounts for the approximately 80% loss of DA in the striatum (Zigmond & Burke, 2002). This means that one of major dopaminergic pathways in the human brain, the nigro-striatal pathway, is compromised in PD. This impairment brings to an overall dysfunction of the BG activity and results in the typical motor symptomatology of PD (see table 3.1).

TABLE 3.1 Motor manifestations of Parkinsonism: *Cardinal signs of PD.

Tremor at rest*
Rigidity*
Bradykinesia*
Loss of postural reflexes*
Hypomimia (masked facies)
Speech disturbance (hypokinetic dysarthria)
Hypophonia
Dysphagia
Sialorrhea
Respiratory difficulties
Loss of associated movements
Shuffling, short-step gait
Festination
Freezing
Micrographia
Difficulty turning in bed
Slowness in activities of daily living
Stooped posture, kyphosis, and scoliosis,
Dystonia, myoclonus, orofacial dyskinesia
Neuro-ophthalmologic findings
Impaired visual contrast sensitivity
Visuospatial impairment
Impaired upward gaze, convergence, and smooth pursuit
Impaired vestibuloocular reflex
Hypometric saccades
Decreased blink rate
Spontaneous and reflex blepharospasm (glabellar or Myerson's sign)
Lid apraxia (opening or closure)
Motor findings related to dopaminergic therapy
Levodopa-induced dyskinesia (chorea, dystonia, myoclonus, tic)

(from Jankovic, 2007)

The loss of dopaminergic neurons and the consequent impairment of BG activity do not affect only motor functions. As mentioned above, BG are not only involved in motor regulation: several researches suggest that BG activity is also related to a variety of cognitive functions, especially working memory and learning abilities (for recent reviews see Helie et al. 2013; Steiner & Tseng, 2010). Furthermore, neuron loss in substantia nigra also involves extrastriatal regions. In fact, DA depletion in nigrostriatal pathway affects functionality of the principal target of basal ganglia outflow, i.e. the frontal lobes. The striatum is in fact connected with several areas of the frontal lobes, beyond the motor areas, such as the dorsolateral prefrontal cortex, the lateral and medial orbitofrontal cortex and the anterior cingulate cortex.

In detail, four fronto-striatal circuitries have been described. Each circuitry starts in a specific region of the frontal cortex and innervates different levels of the striatum before being relayed back to its cortical origin, via the thalamus. The activity of these circuits was related to specific functional outcomes, beyond the motor functioning. While the dorsolateral circuit is associated with high level cognitive functioning, i.e. executive functions (EF), the third and the fourth circuits were related to mood and behavioural regulation (see chapter 1). The original neuron loss in the substantia nigra and then in the striatum inevitably influences the functioning of these circuits and leads to a complex pattern of functional consequences in PD patients.

In addition to the dysfunction of nigro-striatal and fronto-striatal connections, the DA depletion in the substantia nigra also affects another important dopaminergic transmission, represented by the meso-cortico-limbic dopaminergic pathways. In these pathways, DA is transmitted from the ventral tegmental area, located in the midbrain, to several cortical and subcortical structures (see figure 3.2). In detail the following structures are considered to be part of the meso-cortico-limbic dopaminergic pathways: the limbic system, the nucleus accumbens, i.e a structure located in the ventral striatum, the amygdala, the hippocampus and the medial prefrontal cortex. This complex dopaminergic transmission is considered one of the most important anatomical substrates of reward processing and, consequently, of mood and motivational regulation (Wise, 2002-1998; Willner, 2001).

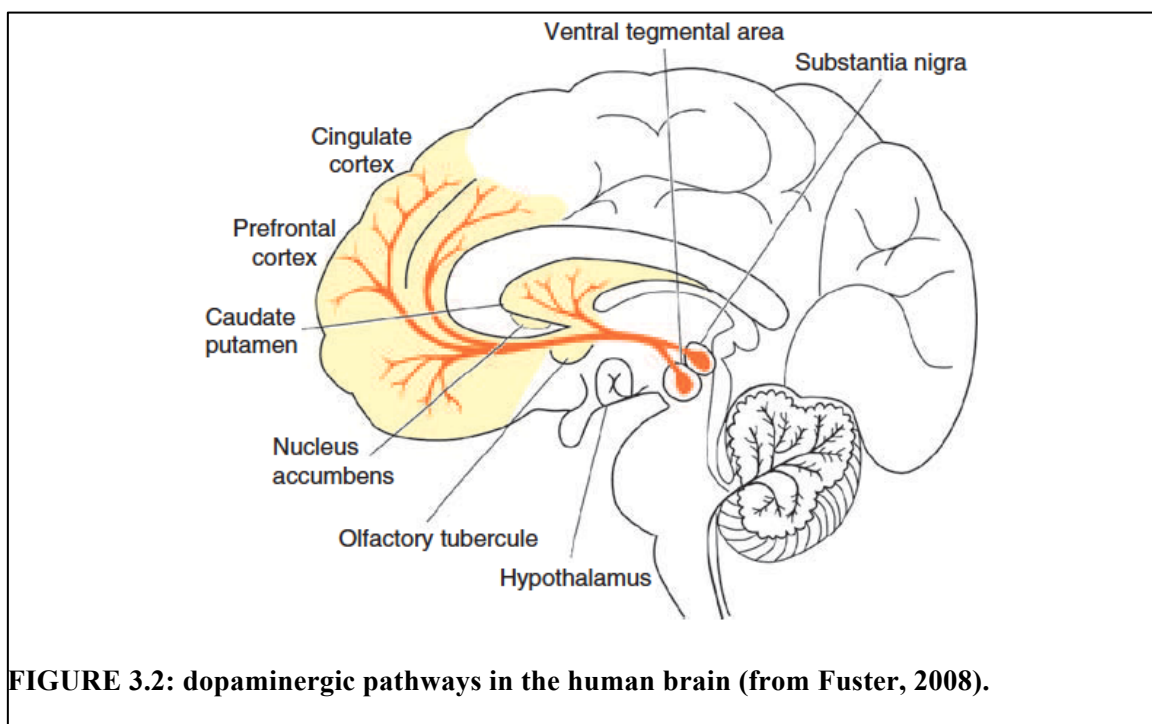


FIGURE 3.2: dopaminergic pathways in the human brain (from Fuster, 2008).

In PD, this pattern of both subcortical and cortical dopaminergic dysfunction is also accompanied by the impairment of different neurochemical systems and neural circuitries. Neuron loss is in fact not restricted to the dopaminergic neurons. Other catecholaminergic cell groups, including the locus coeruleus, are involved, and also some cells of the sympatho-adrenal system and the serotonergic neurons of the raphe nuclei are subject to impairment. Furthermore, a loss of cholinergic neurons in the nucleus basalis of Meynert was also described in PD (for a review see Bohnen & Albin, 2011).

Finally, the cell loss is also accompanied by the presence in the remaining neurons of Lewy bodies, abnormal aggregates of protein that represent another common feature in this pathology. For all of these reasons, even though the DA deficit is a hallmark of this neurodegenerative disorder, it is now generally accepted that PD has a widespread effect in all the nervous system. This extensive involvement can explain the multifaceted symptomatology of PD and it supports the idea that motor symptoms represent only an aspect of this pathology. In fact, even if the diagnosis of PD requires that two of the four primary motor symptoms are present (see table 1) and respond to anti-parkinsonian medication (Jankovic, 2008), non-motor manifestations represent a common feature of PD (see table 3.2). Furthermore, some of these non-motor manifestations may actually precede the motor dysfunction (Bonnet & Czernecki, 2013; Dickson et al., 2009).

Table 3.2 Principal non-motor features of Parkinson's disease.

Autonomic dysfunction

Cognitive deficits

Mood disorders

Behavioural disorders

Dementia and psychosis

Sleep disorders

Olfactory dysfunction

Restless legs syndrome

Pain

(adapted from Poewe, 2008)

Of the vast range of non-motor symptoms, cognitive problems can have a significant impact on the quality of life of PD patients. Research in this field is currently aiming to explore the origins and the exact manifestation of these problems, and studies are investigating the potential role of dopaminergic medications in the development of both cognitive and behavioural complications (Vaillancourt et al., 2013; Tang & Strafella, 2012).

3.2 Cognitive deficits in Parkinson's disease: the role of executive functions

Even if James Parkinson described PD as a condition in which “the senses and intellect being uninjured”, now PD is clearly associated with the development of cognitive and behavioural problems. Exploring cognitive functions in PD patients, the severity of the impairment ranges from difficulties in a single domain, through global decline and dementia. In PD different cognitive domains may be impaired, including memory, language, attention, visuospatial and visuo-constructive abilities, and executive functions (EF) (Zgaljardic et al., 2003).

According to literature, the most part of cognitive deficits reported in PD may actually be the manifestation of an underlying executive dysfunction, which seems to be the most important cognitive impairment in this neurodegenerative disease (for reviews see Dirnberger & Jahanshahi, 2013; Parker et al., 2013; Kudlicka et al., 2011). EF deficits affect roughly 30% of PD patients (Parker et al., 2013; see also Aarsland and Kurz, 2010; Williams-Gray et al., 2009) and are considered as predictors of dementia onset in this clinical population (Aarsland & Kurz, 2010; Mahieux et al., 1998; Levy et al., 2002a-b; Janvin et al., 2005). Furthermore, EF deficits are associated with considerable morbidity (Williams-Gray et al., 2007) and seem to predict future mortality of PD patients (Forsaa et al., 2010; Santangelo et al., 2007). Even though such deficits can occur early in the disease (Aarsland et al., 2009; Foltynie et al., 2004) and are linked with gait-disturbance (Wylie et al., 2012), they are not directly correlated with motor dysfunctions (Van Spaendonck et al., 1996). The results of a recent meta-analysis provide consistent evidence for PD impairment of EF as cognitive flexibility, set switching, inhibition and working memory (Kudlicka et al., 2011).

This is not surprising since the above-mentioned degeneration of fronto-striatal connections in PD. Specifically, these evidences are coherent with the impairment of the circuitries that link striatum with the prefrontal cortex, especially the dorsolateral one (Owen, 2004).

Moreover, a different class of EF are also impaired in this clinical condition. PD patients fail in appropriate decision-making on the basis of positive and negative outcomes, making less profitable decisions (Mimura et al., 2006) and showing an overall impairment in the reward driven goal-directed behaviour (Ravizza et al., 2012). This kind of EF impairment has been related to an anomalous reward processing, a deficit that has been documented in PD patients (Kapogiannis et al., 2011; Kobayakawa et al., 2010; Bodi et al., 2009; Rutledge et al., 2009; Frank et al., 2007-2004; Goerendt et al., 2004; König et al., 2000).

While the first class of EF impairment was associated with a dysfunctional dorsolateral-striatal-circuitry, this kind of cognitive disorders are mostly associated with different fronto-striatal circuitries as well as with the degeneration of the meso-cortico-limbic dopaminergic systems.

Despite this pattern of results is based on a large amount of evidences, research of EF deficits in PD is still characterized by different challenges.

From one hand, the complex nature of the EF construct, together with the low validity and reliability of EF tests can give reason of contradictory reports in the literature about EF, and in research about EF in PD (Kudlicka et al., 2011). From the other hand, the clinical heterogeneity and the complex pathology of PD was often considered as responsible for this inconsistent literature. Current research is now highlighting the importance of another factor, i.e. the dopaminergic therapy commonly used for the treatment of motor symptoms in PD.

Motor symptoms of PD are in fact mostly treated with a pharmacological therapy that replaces the lack of DA. Even if a definition of the best pharmacological management in this pathology is still matter of debate (Worth, 2013), Levo-dopa represents the goal-standard in the treatment of PD (Pilleri & Antonini, 2014), being the most effective pharmacologic agent and the primary treatment for symptomatic patients (Rao et al., 2006). Levo-dopa is a metabolic precursor of DA that crosses the blood-brain barrier, is converted in DA and acts as a replacement of the dopaminergic lack.

Due to side effects of a prolonged administration (for details about “long-term levodopa syndrome” see Factor, 2007), levo-dopa is usually prescribed with adjunctive therapies, of which DA-agonists represent the most common. Without going into details about chemical aspects, one common feature of these pharmacological therapies is the action on the DA system that improves the functioning of DA neurons activity.

Recent studies have found that the dopamine replacement therapy (DRT) classically ameliorates motor deficits in PD, but it can also affect on non-motor manifestation of PD, such as cognitive deficits. Evidence report that DRT could improve and impair the cognitive performance of PD patients (Kulisevsky et al., 2007-1996; Robbins, 2005; Cools et al., 2003-2001; Kulisevsky, 2000) and this double effect seems to be dependent on several factors. For example, DRT effects on cognitive functions could be different depending on the individual DA genotype, which is related to the individual differences in the response to the DRT. Additionally, DRT effects on cognitive functions are due to the different levels of DA depletion in different brain areas. In detail, the fact that a more pronounced reduction of DA concerns the dorsal than the ventral striatum in PD (Kish et al., 1988) can bring to differential effects of the DRT on the neural circuits that involve these regions. In this way, therapies that restore dopaminergic level in the dorsal fronto-striatal connections could result in a dopamine “overstimulation” in the ventral fronto-striatal connections, bringing to differential effects on the cognitive functions related to those circuits. Coherently with this assumption, recent findings suggest that while DRT ameliorates the performance in the tasks associated with the dorsal fronto-striatal circuitry (Sohn et al., 2000), it impairs the performance in the task related to relatively less compromised areas, as the ventral fronto-striatal one (Cools et al., 2003). Particularly, several evidence reported that patients with mild to moderate disease are impaired in planning and task switching when DRT is withdrawn (‘off’ state), but they are not impaired on risk-taking paradigms or probabilistic reversal learning (Foltynie et al., 2004a,b; Cools et al., 2003-2001; Lewis et al., 2003; Swainson et al., 2000; Gotham et al., 1988). On the contrary, when treated with dopaminergic agents (‘on’ state) planning and task-switching deficits improved, but PD patients become impaired on risk-taking, gambling and reversal learning paradigms (Pagonabarraga et al., 2007; Voon & Fox, 2007; Mimura et al., 2006; Brand et al., 2004; Cools et al., 2003-2001; Molina et al., 2000; Swainson et al., 2000) and manifests feedback processing abnormalities (Kapogiannis et al., 2011; Bodi et al., 2009; Kobayakawa et al., 2010; Frank et al., 2007-2004).

These results seem to be consistent with the “dopamine overdose hypothesis” (Cools et al., 2001; Swainson et al. 2000; Gotham et al., 1988), which suggests the presence of a DA overstimulation by DRT in the relatively intact DA-dependent brain regions.

Even if cognitive functions have been the major focus of research about the dopamine overdose hypothesis, overstimulation by DRT has been also related to the development of impulse control disorders (ICDs) in PD patients. According to the DOMINION study (Weintraub et al., 2010), most frequent ICDs in PD patients under DRT are compulsive shopping, pathological gambling, binge eating and hyper sexuality. The development of these disorders, by around 15% of medicated PD patients (Callesen et al. 2013), has been linked to the overstimulation of the mesolimbic dopaminergic system (Cools & Robbins 2004). In detail, several lines of evidence point toward a reduced sensitivity of the reward system as a key feature in the development of ICDs by PD patients under DRT (for a review see Callesen et al. 2013). Linking cognitive deficits to these behavioural outcomes, it could be reasonable that feedback-processing deficits generally result in aberrant expectations of reward and loss and, consequently contribute to the development of pathological behaviour as ICDs.

The exploration of DRT effect on cognitive functions of PD patients is object of several investigations, with particular interest in the understanding of the relation between EF deficits and dopaminergic treatment (for a review see Vaillancourt et al., 2013).

In our opinion, in stead of “overdose”, the term “dysregulation” better describes the complex DA functionality in PD, and better summarizes the positive and the negative results of the complex interaction between individual differences, pathological factors and pharmacological treatment.

The above described findings of PD-related deficits in working memory, planning, inhibition and task- or set-switching, as well as in reward based control of behaviour, represent a set of evidence that should still be explored and investigated, trying to better define the EF profile of medicated PD patients. This is the goal this thesis. Aim of the three studies that will be presented is to investigate EF deficits in medicated PD patients, trying to add evidence and to improve our understanding by employing new methodological approaches.

CHAPTER IV - FIRST STUDY

EXECUTIVE FUNCTIONS AND WORKING MEMORY: INTERFERENCE AND FACILITATION EFFECTS IN AGEING AND IN PARKINSON'S DISEASE

4.1 Introduction

Working memory (WM), as proposed by Baddeley (Baddeley & Hitch, 1974; Baddeley, 1986), is a powerful explanatory concept that includes some of the fundamental properties of short term memory, like the capacity to store information for a brief period of time, together with the presence of a superordinate control system that permits the use of stored information in the service of complex cognitive tasks. According to one of the most adopted models in cognitive psychology (Baddeley 2000-1986) WM is described as the implementation stores and rehearsal processes of short term memory, that maintain information in active state, and executive processes that enable work to be done with the stored contents (Miyake & Shah, 1999). This kind of model is not contrasting with functional neuroimaging studies, which interpret WM process as the result of an interaction across different brain regions in extended networks. WM performance would reflect the integration of “top-down” signals from prefrontal cortex (PFC) and posterior brain regions (Desimone & Duncan, 1995), contributing to the encoding, maintenance, and retrieval of representations in WM (Sander et al., 2012; Miller & Cohen, 2001).

Both cognitive and neurocognitive models agree in defining WM performance as the “outcome of processing at multiple hierarchical levels, including the analysis of low-level features and their integration or binding into higher-level representations in interaction with top-down control processes to reconstruct a stable mental representation of previously experienced information” (Ranganath, 2006). This tight integration of the storage and processing components of the WM system provides functionality in higher cognitive domains, such as planning, problem-solving, and reasoning (Braver & West, 2008).

The research on WM has mostly upheld these assumptions but this concept is still evolving, especially in terms of exploration of the mental operations that make up the central executive (Smith & Jonides, 1999; Goldman-Rakic, 1995; Petrides, 1994). Despite the complex issue of defining executive function (EF), according to Reuter-Lorenz and Sylvester (2005) there is a common agreement in taking into account at least four key processes crucial to the “top-down” operations of WM: *executive attention*, that focuses resources on task relevant information and *inhibition*, that suppresses irrelevant information and resolves interference and conflict; *task management*, i.e. the ability to maintain a goal and organize sub-goals and, finally, *set shifting* which refers to the ability to change rule states and decision criteria.

Following the current challenges in defining the precise role of such executive operations in WM, goal of the present study is to examine mostly the role of executive attention and inhibition components. We propose a new task, which aims at exploring the focusing of attention on the WM representations, referring to studies that showed as selective attention operates in a similar way to both perceptive and symbolic representations (Chun, 2011; Cherubini et al., 2007; Cherubini et al., 2006). More precisely, we translated a classical paradigm used for the study of attention, the Stroop task (Stroop, 1935), in a WM task, using symbolic instead of perceptual stimuli. In detail, the task was designed using condition-action rules as stimuli, and supposing that an irrelevant bi-conditional rule (“if X occurs, then do Y; otherwise do Z”), transiently encoded in WM, can affect the use of a similar task-relevant rule that is also stored in WM. Setting up two congruence conditions, as happens with the stimuli of the Stroop task, incongruence between the two rules should cause significant interference effects measured as delays in reaction times (RT) and lower accuracy, while a congruence should result in facilitation effect, i.e. faster RT and higher accuracy.

In the present study we propose the application of this new WM task in healthy young, adults and older people and in a sample of Parkinson’s disease patients under dopaminergic treatment.

First aim of this study is to explore the top-down components of WM, investigating how executive attention and inhibition works in the management of symbolic information in WM. Secondly, this study aims at exploring ageing effects on these WM components, supposing that age-related changes in EF would increase vulnerability to interference also in WM (see Reuter-Lorenz & Sylvester, 2005).

Literature about WM and ageing strictly refers to the Baddeley structural distinction between the storage buffers and executive control components. It shows that the tasks which seem to tap best into the function of WM storage buffers show minimal age-differences while, the so-called complex span tasks, which require the coordination of short-term storage with the processing capacity of the executive controller, do show robust and reliable age-differences (Bopp & Verhaeghen, 2007; Bopp & Verhaeghen, 2005; Babcock & Salthouse, 1990). Recent WM literature is advising the use of other forms of testing along with span tasks for the measure of age-related cognitive decline in executive control processes of WM (Braver & West, 2008). In our opinion, our task follows this suggestion, exploring executive components of WM without focusing on a span measure. Finally we will investigate if, and how, top down components of WM are impaired in medicated PD patients, on the base of knowledge about the primary role of the dopaminergic frontal-basal connection in the filtering of irrelevant information in WM (Baier et al., 2010; McNab & Klingberg, 2008; Moustafa et al., 2008; Vogel et al., 2005; Frank et al., 2001; Goldman-Rakic, 1996) and basing on empirical findings about reliable impairments of PD patients in WM task (Lewis et al., 2005; Owen, 2004; Owen et al., 1997; Cooper et al., 1991). In detail, these impairments refer to a significantly lower WM span compared to healthy subjects (Fournet et al., 2000; Stebbins et al., 1999; Fournet et al., 1996; Gabrieli et al., 1996). The findings are also accompanied by neuroimaging data that support the hypothesis of a negative relation between basal ganglia (BG) activity and WM impairment in PD patients (Lewis et al., 2003; Owen et al., 1998) and indicate an involvement of BG in WM tasks in healthy subjects (Chang et al., 2007; Monchi et al., 2000). Even in the study of clinical samples, research efforts are moving towards the separation of executive components and the storage capacity of WM; this trend is followed by both behavioural and neuroimaging studies. For what concerns the study of WM in PD patients, this current trend is also accompanied by the exploration of the role of DA medication, that might either enhance or impair performance in PD patients (for a review see Moustafa et al., 2008).

In conclusion, we will explore the executive components of WM, precisely executive attention and inhibition, investigating these cognitive functions in healthy ageing and in Parkinson's disease. To reach these goals we proposed our new task to three groups of healthy people, one represented by young participants (19-27 years), one represented by adults (55-66 years) and one by older subjects (68-80 years), and to a fourth group of medicated PD patients, matched for age, sex and education with the older subjects.

4.2 Method

Participants

A total of sixty-two healthy participants were recruited in this study: twenty young (7 M; age range 19-27 years; mean= 23.5 sd=2.3) twenty-two adults (13 M; age range 55-66 years, mean= 61.7 sd=3.1) and twenty older subjects (11 M; age range 68-80 years, mean= 71.9 sd=2.5) took part in the experiment. Twenty PD patients (12 M; age range 56-77 years, mean=69.3 sd= 5.9) were also recruited in the Neurology division of the Pederzoli Hospital, in Peschiera del Garda (Verona-Italy). The PD patients fulfilled formal diagnostic criteria for PD according to the Unified Parkinson's Disease Rating Scale (UPDRS; Fahn & Elton, 1987; Goetz et al., 2003); in this group the mean disease duration was of 5.5 years (range of onset 1–14 years, sd= 3.4) and the mean estimated motor sub score on the UPDRS was of 9.9 (range 3.5-2; sd= 4.5).

PD Patients were asked to continue taking their medication at the required time on the day of testing session: nine patients received dopamine precursors (levodopa), two patients were receiving dopamine agonists, three received a monoamine oxidase inhibitor (MAOI) and five patients were taking a combination of levodopa and dopamine agonists. PD patients and older subjects were matched for age, gender and education (see table 4.1). Participants gave signed informed consent after the purpose of the study and the protocol had been explained to them.

Exclusion/Inclusion criteria. Inclusion criteria for this study were participants with normal or corrected to normal vision. Exclusion criteria applied for the recruitment of healthy participants were the presence of neurological disease (any medical conditions associated with a head injury, epilepsy, stroke), reported history of psychiatric disorder or neurological disease and use of psychiatric and neurological medications. Additionally, for adult, old and PD patients exclusion criterion was a Mini Mental State Examination (MMSE; Folstein et al., 1975) score under the cut-off (24).

TABLE 4.1 Means and standard deviations of the demographical characteristics of the four groups. Tests refer to the match between old subjects and PD patients.

	Young ¹ N= 20	Adults N= 22	Old N= 20	PD patients N= 20	test (df)	p- value
Age (years)	23.5 ± 2.3	61.7 ± 3.1	71.9 ± 2.5	69.3 ± 5.9	t _(25.4) =1.81	ns
Gender	7 M	13 M	11 M	12 M	χ ² ₍₁₎ =.102	ns
Education(years)	15.9 ±1.4	7.4 ± 3.4	6 ± 3	7.1 ± 3.4	t ₍₃₈₎ =-1.08	ns

Notes: Variations on degrees of freedom (df) in t-test calculation are due to significant Levene test.

Measures

Neuropsychological assessment. Old participants and PD patients were invited to attend a neuropsychological assessment session. In detail, after the screening with MMSE (Folstein et al., 1975) that assessed the study eligibility, the following standardized tests were administered. Phonemic fluency test and Brown Peterson technique (10” and 30”) tasks were selected from the battery Esame Neuropsicologico Breve-2 (ENB2, Mondini et al., 2011), to evaluate respectively verbal production and response generation and short term memory in condition of interference. The Frontal Assessment Battery (FAB; Dubois et al., 2000; see also Apollonio et al., 2005) was also administered, to have a global index of EF. Testing materials are reported in Appendix.

Experimental task. The experimental design of the new task employed in the present study is described in figure 4.1. The experiment ran with the E-Prime 2 software (Psychology Software Tools, Pittsburgh, PA) installed on a personal computer equipped with a 17” monitor. The general structure of the task was the following: two condition-action biconditional rules (“if X occurs, then do Y; otherwise do Z”), independent and categorized with the A or B, were presented at the center of the screen. In these rules only one of three geometrical figures, a circle, a square or a triangle, was associated with a response key. Participants were asked to learn both rules and the duration of this learning phase was self regulated by every participants.

¹ Data collected in collaboration with Michele Burigo, Doris Pischedda and Paolo Cherubini

When they declared to have learned the two rules, one of the two letters, A or B, were presented as cue, indicating which of the two rules become relevant for the task; participants were then asked to associate the current trial, a trigger stimulus represented by one of the three geometrical figures, with the appropriate response key. Participants responded using the left or the right button of an analogue computer mouse, labelled with the number 1 and 2 in a counterbalance way across participants.

In detail, the trigger stimulus was classified as relevant if it matched the condition of the cued rule; critical if matched the condition of the uncued rule and neutral if it did not match the condition of any rule; In addition the two rules were classified as congruent or not: the congruence depended on the response suggested to the critical triggers by the two rules presented; during congruent trials the uncued rule suggested the appropriate response to the critical trigger while during incongruent trials the irrelevant rule suggested inappropriate response to the critical trigger.

Six experimental conditions originated from a fully orthogonal 2x3 within-participants factorial design, which includes two congruence condition (congruent vs. incongruent trials) and three relevance conditions of the trigger figure (relevant, critical and neutral). As result of all possible combinations between congruence of trial (congruent or incongruent), key responses (key 1 or key 2), cues (A or B) and trigger figures (triangle, square, or circle) 144 trials in the experimental session were presented. Trials in which the two rules had the same condition were omitted. The experimental session was structured in this way: after participants read self-paced instructions displayed on a computer, two blocks of practice trials were administered. In the first practice block participants were trained on how to interpret each task rule. Only one rule at a time was displayed, no cue was presented, and an accuracy feedback was given after each response. The practice block ended as soon as the participant provided five correct responses across the final six trials. In the second practice section, detailed instructions about the two-rules structures were described, explaining how to interpret the cue that follow the learning phase. Participants were explicitly told that only the cued rule should govern responses, while the uncued rule was irrelevant and must be ignored. After five practice trials, randomly selected from the 144 experimental trials, the experimental phase started.

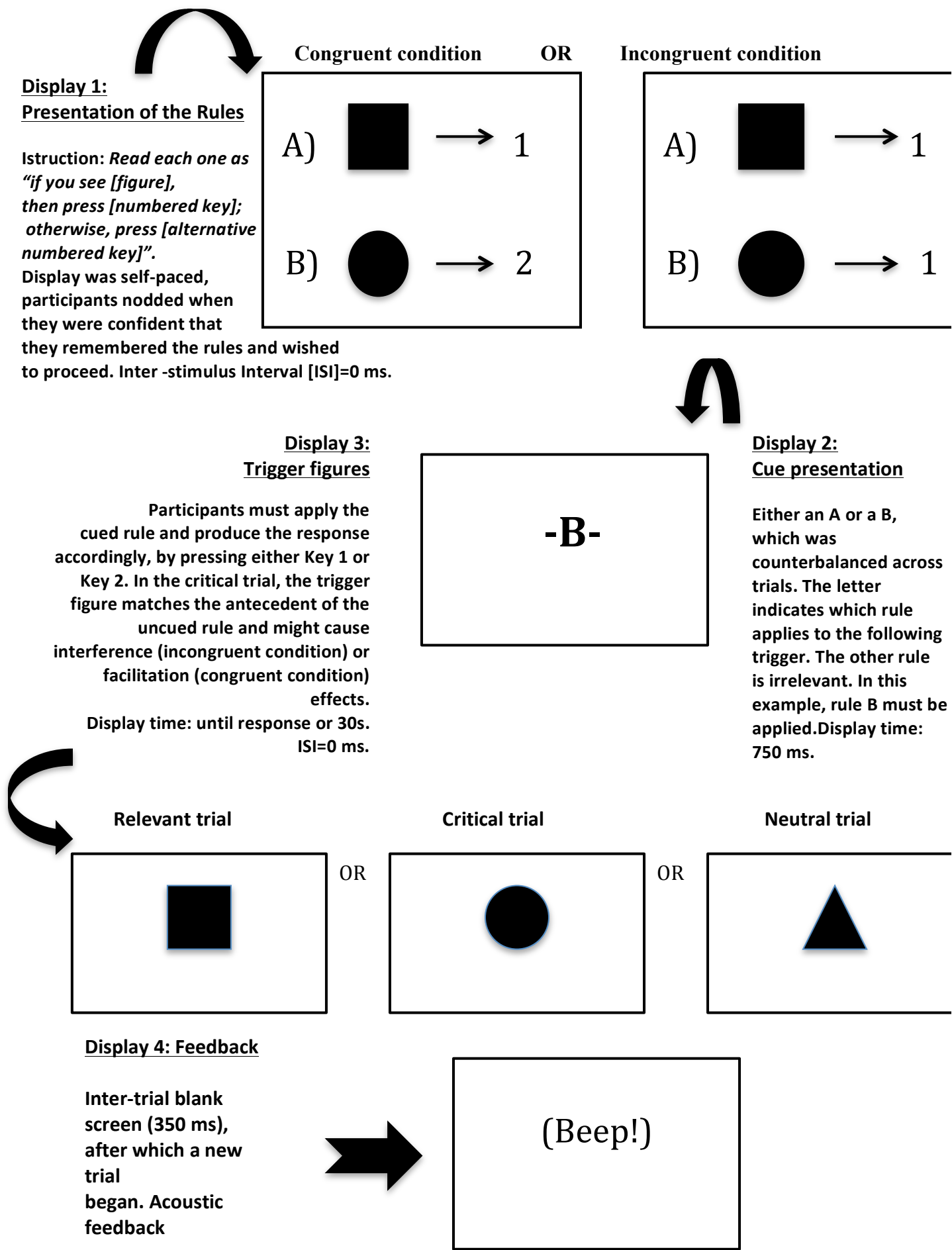


FIGURE 4.1: the experimental design with examples of each type of trial and congruence conditions.

Data analysis

Preliminary analyses of response times (RT) and accuracy rates were performed with the aim to evaluate group's differences in terms of speed and accuracy. These raw data were submitted to a repeated measure ANOVA 2 (condition: congruent vs incongruent) x 3 (trigger: relevant, critical and neutral) x 4 (group: young, adults, old and PD patients). Participants' RT and accuracies were also submitted to the normalization procedure (see figure 4.2), in order to calculate pure measure of facilitation and interference. Using this normalization procedure, which removes the effects of differences in terms of absolute speed and accuracy, it is possible to obtain conservative indices of facilitation and interference by the contrast of normalized critical vs. neutral trials. In this way, pure measures of the effect of the irrelevant rule on the response are obtained. Normalized accuracy rates and response times were submitted to different repeated measure analysis of variance (rANOVA), with the within subject factors condition (congruent vs incongruent) and trigger (critical vs neutral), and considering group (young, adults, old and PD patients) as between subject factor.

Normalized RT Critical trigger: *Mean RT critical trigger/ Mean RT relevant trigger*

Normalized RT Neutral trigger: *Mean RT neutral trigger/ Mean RT relevant trigger*

Normalized accuracy Critical trigger: *Accuracy critical trigger/ Accuracy relevant trigger*

Normalized accuracy Neutral trigger: *Accuracy neutral trigger/ Accuracy relevant trigger*

FACILITATION AND INTERFERENCE EFFECTS CALCULATION

Facilitation

$\Delta RT = (\text{Normalized RT congruent Critical trigger}) - (\text{Normalized RT congruent Neutral trigger})$

$\Delta \text{Accuracy} = (\text{Normalized accuracy congruent Critical trigger}) - (\text{Normalized accuracy congruent Neutral trigger})$

Interference

$\Delta RT = (\text{Normalized RT incongruent Critical trigger}) - (\text{Normalized RT incongruent Neutral trigger})$

$\Delta \text{Accuracy} = (\text{Normalized accuracy incongruent Critical trigger}) - (\text{Normalized accuracy incongruent Neutral trigger})$

Figure 4.2: normalization procedure for response times and accuracy rates

4.3 Results

Neuropsychological assessment

Mean performances of old subjects and PD patients are reported in table 4.2. Results of a between groups comparison revealed that, in spite of the absence of differences in the MMSE scores, PD patients had significant lower FAB total score and they had lower scores in BPT 10'' and 30'' tests. On the contrary, the mean number of words pronounced in the phonemic fluency test was not different between the two groups, indicating comparable response generation and verbal production.

TABLE 4.2 Neuropsychological assessment. Mean scores and standard deviations of old subjects and PD patients' performance.

	Old N=20	PD patients N=20	t test (df)	p-value
MMSE	28.5 ± 1.05	27.8 ± 1.5	1.53 (31)	ns
FAB	15.5 ± 1.83	13.9 ± 2.4*	2.21(38)	.033
Phonemic fluency	8.25 ± 2.4	9.01 ± 4.1	-.71 (30.3)	ns
BPT 10''	6.6 ± 1.7	5.1 ± 2.8*	2.05 (31.6)	.047
BPT 30''	6.5 ± 1.8	4.7 ± 2.8*	2.43 (33.1)	.020

Notes: Variations on degrees of freedom (df) calculation are due to significant Levene test. MMSE: Mini-Mental state examination; FAB: frontal assessment battery; BPT: Brown Peterson technique. In the phonemic fluency the score represents the mean number of words pronounced.

Experimental task

Raw response times and accuracy rates at relevant, critical and neutral trial are reported in the table 4.3. In the same table are also reported facilitation and interference effects calculated following the normalization procedure (see figure 4.2).

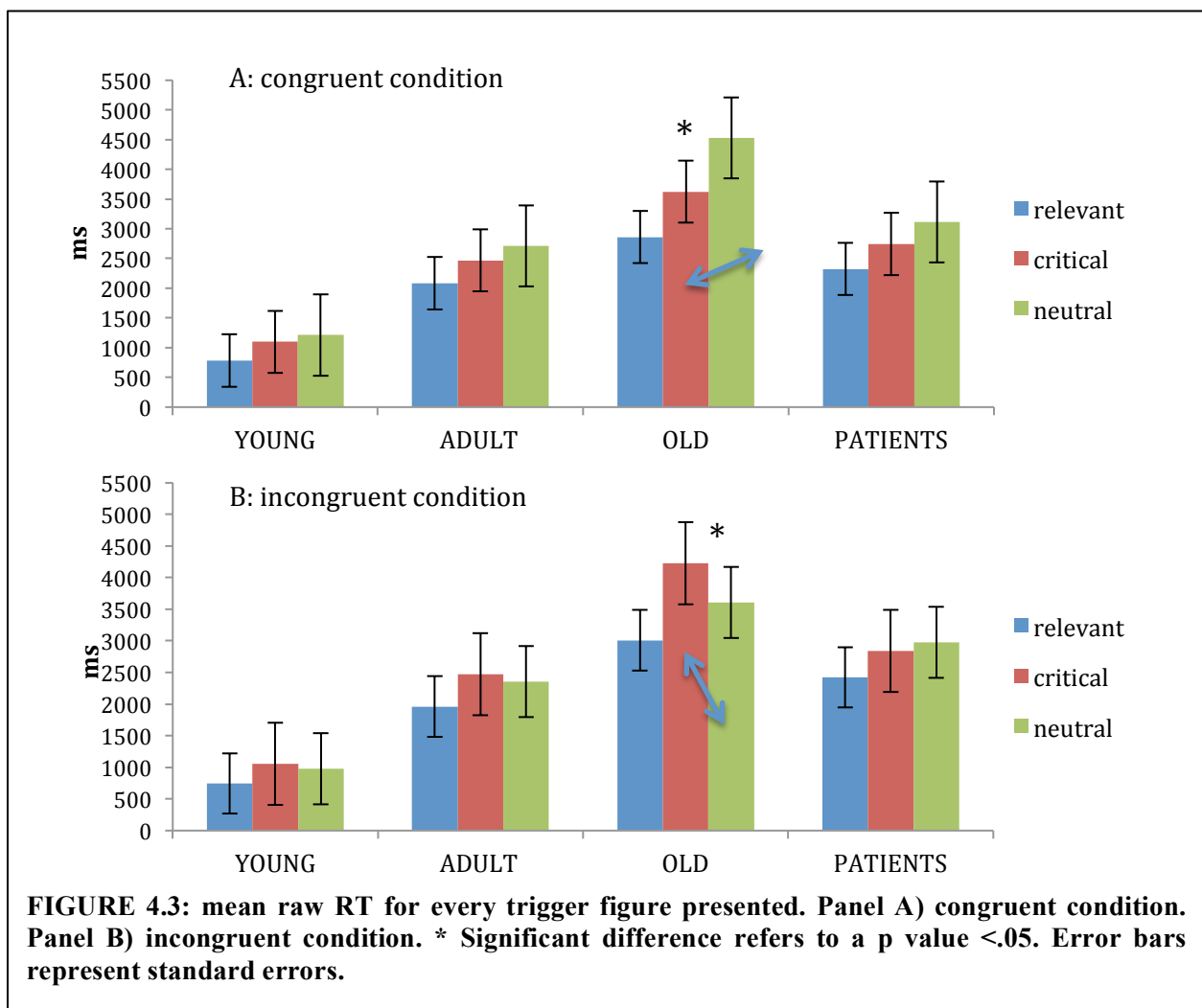
TABLE 4.3 Raw response times and accuracy rates (mean and standard deviations). Facilitation and interference measures are also provided.

Group	Condition	Response times (ms)	Δ RT (ms)	Accuracy (%)	Δ Accuracy (%)
Young	Congruent	Relevant: 782.9 \pm 229 Critical: 1097.3 \pm 276 Neutral: 1210.3 \pm 340	Facilitation -9	Relevant: 91 \pm 2 Critical: 86 \pm 3 Neutral: 85 \pm 4	Facilitation +0,8
	Incongruent	Relevant: 745.1 \pm 258 Critical: 1057.1 \pm 344 Neutral: 974.4 \pm 290	Interference +2	Relevant: 91 \pm 3 Critical: 84 \pm 4 Neutral: 92 \pm 4	Interference -9
Adult	Congruent	Relevant: 2083 \pm 219 Critical: 2467.7 \pm 263 Neutral: 2713.8 \pm 324	Facilitation -10	Relevant: 76 \pm 3 Critical: 72 \pm 3 Neutral: 70 \pm 3	Facilitation +0,5
	Incongruent	Relevant 1960.2 \pm 246 Critical: 2474.7 \pm 328 Neutral: 2357.1 \pm 277	Interference + 8	Relevant: 77 \pm 3 Critical: 63 \pm 4 Neutral: 74 \pm 4	Interference -15*
Old	Congruent	Relevant: 2859.4 \pm 229 Critical: 3622.7 \pm 276 Neutral: 4530.4 \pm 340	Facilitation -53*	Relevant: 72 \pm 3 Critical: 59 \pm 3 Neutral: 47 \pm 4	Facilitation +18*
	Incongruent	Relevant: 3005.1 \pm 258 Critical: 4223.4 \pm 344 Neutral: 3607.1 \pm 290	Interference + 16	Relevant: 69 \pm 3 Critical: 48 \pm 4 Neutral: 63 \pm 4	Interference -21 *
Patients	Congruent	Relevant: 2322.5 \pm 229 Critical: 2743.7 \pm 276 Neutral: 3116.9 \pm 340	Facilitation -17	Relevant: 70 \pm 3 Critical: 62 \pm 3 Neutral: 52 \pm 4	Facilitation +10*
	Incongruent	Relevant: 2422.1 \pm 258 Critical: 2842.7 \pm 344 Neutral: 2977 \pm 290	Interference -4	Relevant: 62 \pm 3 Critical: 45 \pm 4 Neutral: 63 \pm 4	Interference -26 *

Notes: $\Delta = [(critical\ trigger/ relevant\ trigger) - (neutral\ trigger/ relevant\ trigger)]$; * Significant difference refers to a p value $<.05$.

Response times

Raw values. Results of raw response times analysis yielded a main effect of group [$F(3,78)=18.75$ $p=.001$ $n_p^2 = .419$], that indicated increasing RT from adult to old and patients group, comparing with the young participants, but non significant differences between PD patients, adult and old groups. The same analysis revealed a main effect of trigger [$F(2,156)=34.04$ $p=.001$ $n_p^2 = .30$] and a significant interaction trigger*condition [$F(2,156)=11.53$ $p=.001$ $n_p^2 = .129$], showing slower RT for neutral triggers, especially in congruent condition. The significant interaction trigger*condition*group [$F(6,156)=3.23$ $p=.01$ $n_p^2 = .11$] showed that this modulation of neutral trigger responses by conditions is significant only in the old participants, who modulated also critical trigger responses depending on condition. Furthermore, post hoc comparisons indicated that only old participants showed a significant difference between critical and neutral trigger in both conditions, in terms of absolute values of response times (see figure 4.3). The analysis of normalised data, which permits the evaluation of facilitation and interference effects, was then conducted to confirm these results.



Normalized values. Results of the normalised response time analysis showed a significant but small effect of condition [$F(1,78)=4.07$ $p=.047$ $\eta_p^2 = .05$] and a significant interaction trigger*condition [$F(1,78)=13.12$ $p<.005$ $\eta_p^2 = .14$]. Post hoc comparisons indicated that if compared with the neutral trigger, critical triggers bring to a different response depending on the condition: in congruent conditions it manifests a significant facilitation effect ($p<.01$), while in incongruent conditions the direction is the opposite, close to an interference effect ($p=.058$). The triple interaction trigger*condition*group was not significant [$F(3,78)=2.37$ $p=.07$ $\eta_p^2 = .08$].

To evaluate the significance of facilitation and interference effect a within group analysis was performed using Fisher test and applying a Bonferroni correction for multiple comparisons. Results indicated that the only significant effect is manifested by the old group, that showed a significant facilitation effect was significant ($p<.005$) but a non significant interference effect ($p=.058$). Young, adult and PD patients group did not show any significant effect in this response times analysis (see figure 4.4).

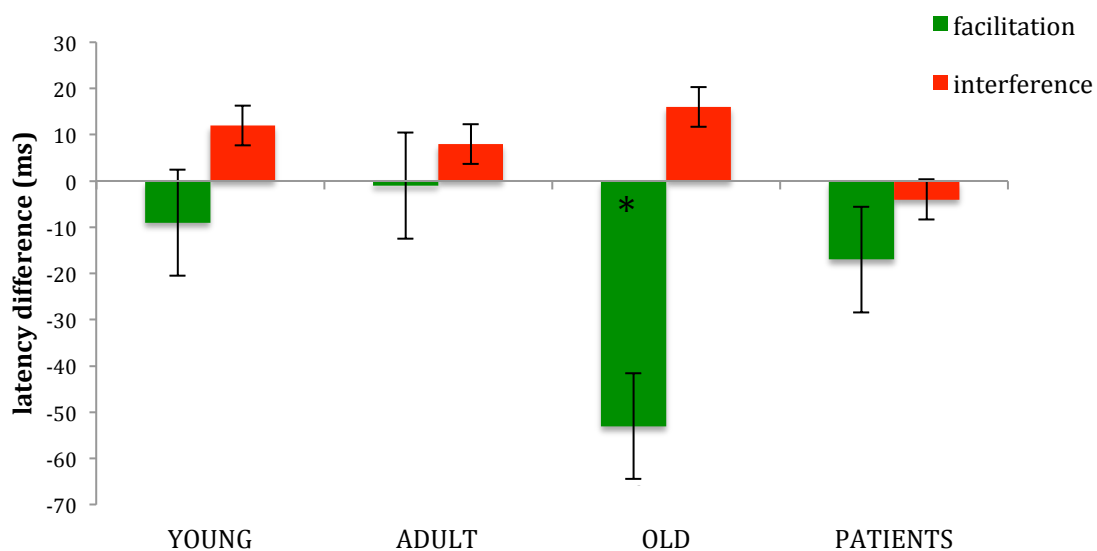


FIGURE 4.4: facilitation and interference effects in the four groups. * Significant difference refers to a p value <.05. Error bars represent standard errors.

Accuracy

Raw values. Results of raw accuracy rates analysis showed a main effect of group [$F(3,78)= 28.7$ $p=.001$ $n_p^2= .52$], that indicated decreasing accuracy rates from adult to old and patients group, comparing with the young participants, but non significant differences between PD patients and old group. As the previous one on raw RT, this analysis revealed a main effect of trigger [$F(2,156)=38.92$ $p=.001$ $n_p^2= .33$], indicating higher accuracy for relevant triggers and lower for critical ones; the significant interaction trigger*condition [$F(2,156)=36.72$ $p=.001$ $n_p^2= .32$] showed that accuracy on critical and neutral trigger is also significantly modulated by condition, with congruent conditions that increase the accuracy of critical response, reducing those of neutral ones (see figure 4.5).

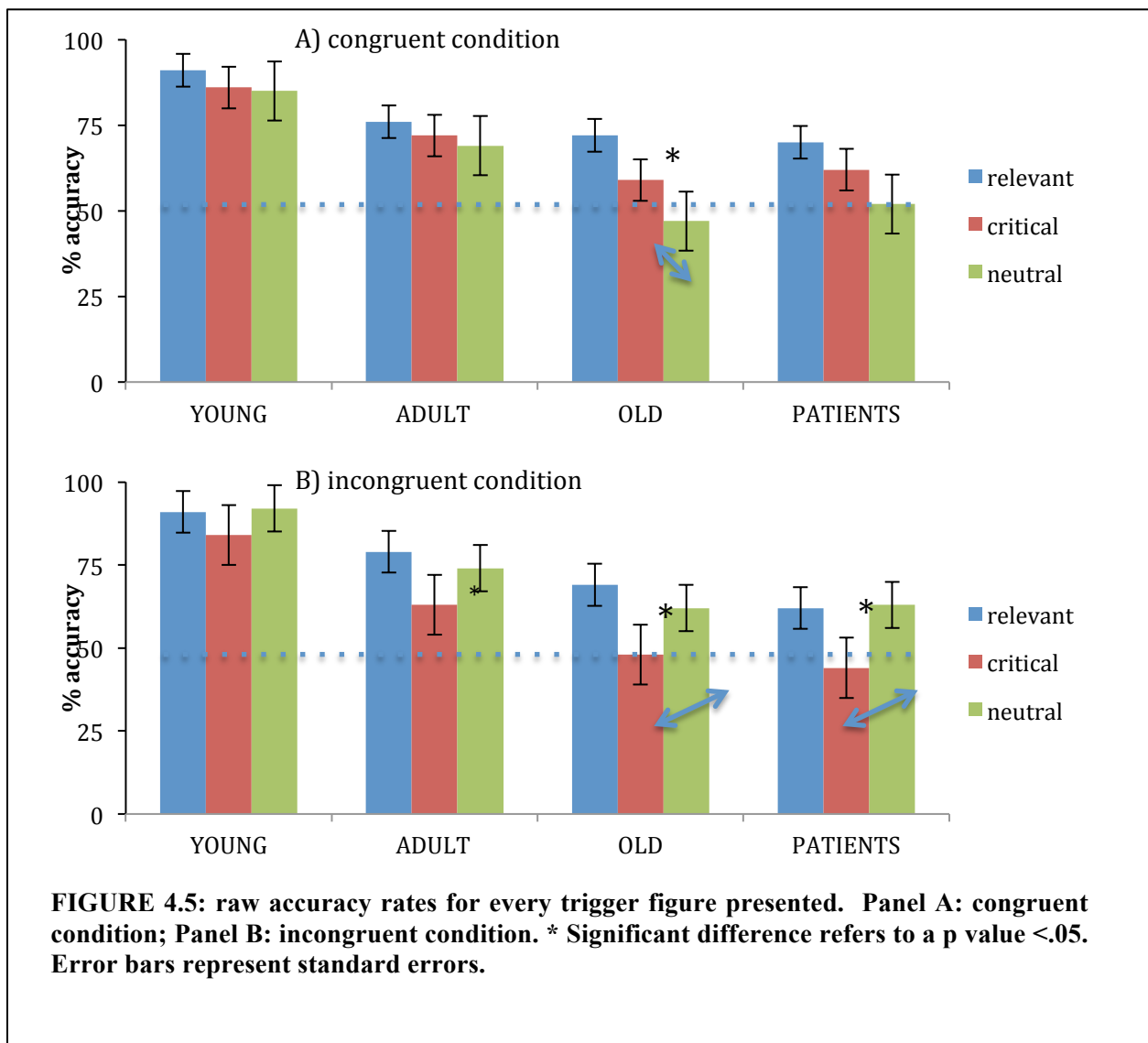
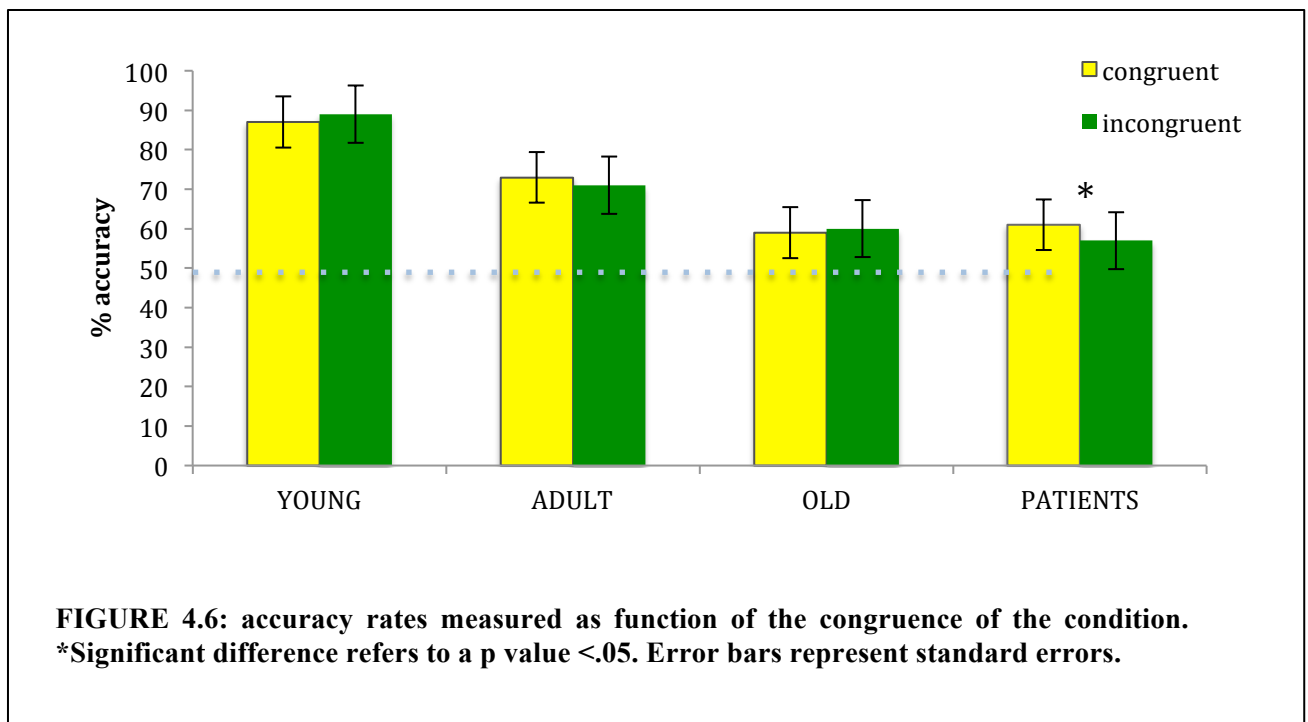


FIGURE 4.5: raw accuracy rates for every trigger figure presented. Panel A: congruent condition; Panel B: incongruent condition. * Significant difference refers to a p value <.05. Error bars represent standard errors.

The significant interaction trigger*condition*group [$F(6,156)=2.59$ $p=.05$ $\eta_p^2 = .09$] showed that the response at critical and neutral triggers are modulated by conditions not in all groups: in fact, while in congruent conditions only old showed a significant difference between critical and neutral responses, in incongruent conditions every group, except young, manifested different accuracy patterns in critical and neutral triggers (see figure 11). Finally, the condition*group significant interaction [$F(3,78)=2.94$ $p=.05$ $\eta_p^2 = .099$] revealed as PD patients were less accurate in the incongruent condition, respect to their performance in the congruent one (see figure 4.6).



Normalized values. The rANOVA on normalized accuracy rates yielded a main effect of group [$F(3,78)= 4.05$ $p<.05$ $\eta_p^2 = .135$] and a main effect of trigger [$F(1,78)= 11.29$ $p<.005$ $\eta_p^2 = .126$], with higher normalized accuracy for neutral triggers (93%) respect to critical ones (86%).

The same analysis revealed also significant interactions: trigger*condition [$F(1,78)= 48.6$ $p<.001$ $\eta_p^2 = .384$] and trigger*condition*group [$F(3,78)= 3.13$ $p<.05$ $\eta_p^2 = .108$]. Using Fisher test to evaluate the significance of facilitation and interference effects, it was shown that while young participant did not show any effect and adults showed only interference, old and PD patients showed both facilitation and interference significant effects (see figure 4.7).

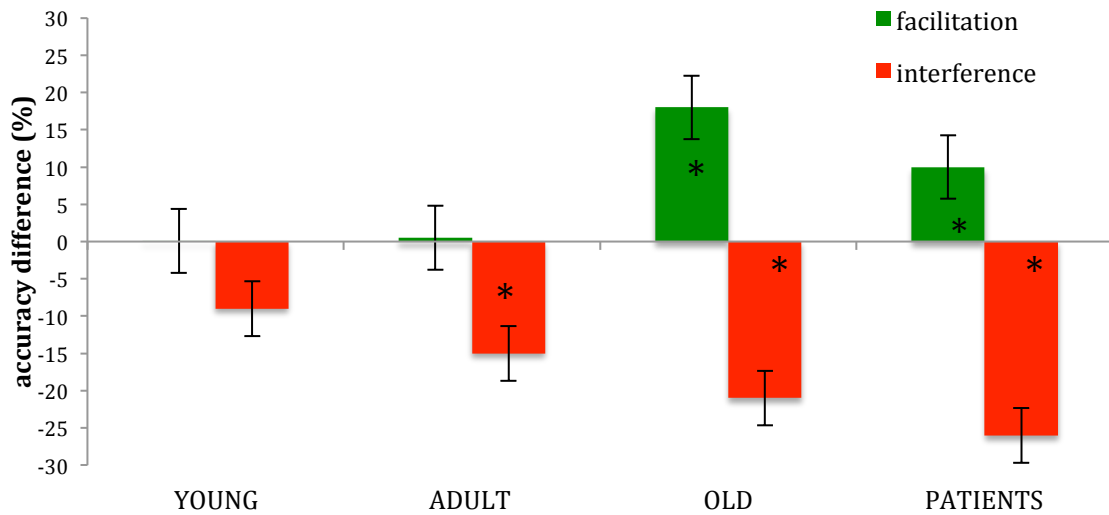


FIGURE 4.7: facilitation and interference effects in the four group. Only old and PD patients showed significant effects. * Significant difference refers to a p value <.05. Error bars represent standard errors.

4.4 Discussion and conclusion

In the present study, a new WM task was applied in young, adults and old healthy people, and in a group of medicated PD patients as well. The first aim of the study was to explore top down components of WM: executive attention and inhibition. In detail the task employed in this study has been designed with the objective of exploring the focusing of attention on WM representations, referring to studies that suggested a cross modal nature of selective attention (Chun et al., 2011; Cherubini et al., 2007; Cherubini et al., 2006). Inspired by a classical Stroop task (Stroop, 1935), in which both relevant and irrelevant stimulus features are simultaneously present and combined in a congruent or incongruent manner, in our task two condition-action biconditional rules (“if X occurs, then do Y; otherwise do Z”), relevant and irrelevant, were designed as congruent or incongruent, with the aim of observing possible facilitation and interference effects in WM, as it happens with conflicting perceptual information (e.g., Stroop effect). To our knowledge this is the first study that explores the critical ability of focusing on a relevant task rule while ignoring or inhibiting irrelevant ones in circumstances in which the rules have just been learned and are transiently encoded in WM.

Second but complementary aim was to exploration of these capacity, executive attention and inhibition in WM, during the lifespan, following the current need to define the nature of the WM decline during ageing. Final aim of the present study was to study the performance of medicated PD patients in this new task, with the objective of exploring top down components of WM in a condition of possible dopaminergic “dysregulation”. Our first prediction was to find increasing facilitation and interference effects during the lifespan, basing on findings about age related vulnerability to interference, and declines in WM (Reuter-Lorenz & Sylvester, 2005). On the other hand, prediction about PD patients’ performance was more difficult to define. On the basis of neuroimaging studies that suggest a primary role of the dopaminergic frontal-basal connection in the filtering of irrelevant information in WM (Baier et al., 2010; McNab & Klingberg, 2007; Vogel et al., 2005; Frank et al., 2001; Goldman-Rakic, 1996) a worse performance of PD patients, compared to healthy controls, was expected, in a task in which selection and inhibition capacities are required. On the contrary, contrasting results about medicated PD patients’ performance in WM tasks (Moustafa et al., 2008) did not permit a specific prediction and suggested a cautious exploration of their performance.

Our results showed that facilitation and interference effects, similar to those obtained in a Stroop task, can be obtained also in reasoning task, where symbolic representations have to be managed and maintained in WM. Irrelevant information, transiently encoded in WM, can affect the response guided by the relevant information. Moreover, the effect of irrelevant information is modulated by its relation with the relevant one, generating facilitation if there is a congruence, and inducing interference if there is incongruence between the responses suggested. These effects are manifested in the latency but also in the accuracy of the responses, where the lack of inhibition of the irrelevant information is manifested with the “capture errors” (Rasmussen, 1982; Reason, 1990). Capture errors, generally described in perceptual domain, in this case do not originate from having omitted a relevant rule but from the inability to inhibit an irrelevant rule, and for this reason represents a valid measure of inhibition capacity. In our cross-sectional analysis, significant interference and facilitation effects emerged in adult and old subjects, indicating that inhibition capacity is not perfectly efficient as it is in younger people. Latency data showed that only old subjects manifest significant facilitation effects; on the other hand accuracy rates showed significant interference effects in adult subjects, and both facilitation and interference in old participants.

This different manifestation of facilitation and interference effects could also support the hypothesis of independence between these two effects (Lindsay & Jacoby, 1994) and, moreover, of different age-related changes in their manifestation. Taken together, results of the application of this new task in healthy people demonstrated that top down components of WM, executive attention and inhibition, seem to follow the same mechanism employed in the attention domain, with the same benefits and costs. Furthermore our task highlighted important ageing effects on these WM components, showing that an age-related decline of inhibition capacity can affect the management of symbolic information in WM.

Results from the application of this task in PD patients showed instead a complex pattern of performance. In the present study we tested a group of PD patients under dopaminergic treatment and we considered the group of old healthy subjects as a matched condition. Both groups were evaluated with standardized neuropsychological tests to exclude general cognitive decline and to compare performance in EF tests and in a demanding short memory test. Results showed that our sample of PD patients, even in absence of generalized cognitive decline, had specific cognitive deficits on EF, like inhibition and abstraction. Furthermore, PD patients manifested a poorer capacity to remember verbal material in conditions of interference. Despite that, results from the experimental task revealed that patients were not slower or less accurate than the control group. From the analysis of normalized values it was possible to observe a complex pattern: while PD patients showed significant facilitation and interference effects measured on accuracy rates, like the control group, they did not show any significant effect measured on RT. This lack of effects on RT, which could represent a preserved control of motor response, is quite surprising, especially considering the absence of difference on RT between PD patients and old subjects. Non-demented PD patients under dopaminergic treatment and with EF deficits seemed to show a better performance, in terms of normalised RT, compared to healthy control subjects without EF deficits. The absence of RT effects in PD patients opens to several interpretations. On one side, the greater task sensitivity to detect facilitation and interference effects on accuracy rates should invite us to a cautious interpretation of latency data. On the opposite side, because of the normalization procedure, every value can be viewed as a pure measure of interference or facilitation independently from the group differences in average performance.

Following this assumption, considering latency data we could conclude that our medicated PD patients showed a better performance and seemed to be less sensitive, in terms of response times, to irrelevant information stored in WM. This is a surprising but plausible conclusion, in the light of the contrasting evidence about the role of dopaminergic medication on different aspects of WM tasks (see Moustafa et al., 2008). However, the same PD patients showed significant facilitation and interference effects in the accuracy rates and, unlike their control group, showed different accuracy rates depending on the congruence of the two information stored.

Performing an unplanned “a posteriori” analysis with the aim of understanding this result, we correlated these raw accuracy rates with scores obtained from neuropsychological assessment. What we found is an interesting correlation between FAB (Dubois et al., 2000; Apollonio et al., 2005) total score and the accuracy rates of the incongruent condition (Spearman $\rho = .35$; $p < .05$). Assuming that most part of the FAB score is made up by items that explore inhibitory control and sensitivity to interference, the result of this additional correlation analysis adds information and could help us in reaching an overall conclusion.

The emergence of significant facilitation and interference effects on accuracy rates, in ageing and PD patients, confirms the assumption that key variable of this WM task is represented by the induction of the so called capture errors (Reason, 1990; Rasmussen, 1982). This type of errors represents a preferable index to evaluate WM executive components in this task. Capture errors permitted to highlight age related declines in top down components of WM, like executive attention and inhibition capacity but also allowed to underline an important feature of PD patients’ performance. PD patients performed worse when there was conflicting information to maintain and to manage in WM, suggesting a different WM storage ability in this clinical sample. This finding could support the hypothesis that BG provide a gate on WM updating, and it is coherent with recent neuroimaging findings that showed as the degree of BG activity is predictive of whether or not irrelevant information is unnecessarily stored in WM (McNab & Klingberg, 2008). Nevertheless, latency data of PD patients suggest further exploration. Due to our experimental design, in which patients were tested only in the “on” phase, we can only suppose that differences in latency were due to an enhancement of motor function by the dopaminergic medication.

Given the increasing literature about the role of dopaminergic treatment in WM performance (for a review see Moustafa et al., 2008; see also Lewis, et al. 2005; Costa et al., 2003; Marini et al., 2003; Owen et al., 1995; Lange et al., 1992; Cooper et al., 1991; Poewe et al., 1991), we can however hypothesize a possible future direction, i.e. the consideration of dopaminergic medication role in this task, with the aim of exploring the relation between dopamine and top down components of WM.

CHAPTER V - SECOND STUDY

EXECUTIVE FUNCTIONS AND FEEDBACK PROCESSING: MOTIVATIONAL INFLUENCES ON COGNITIVE CONTROL IN AGEING AND IN PARKINSON'S DISEASE

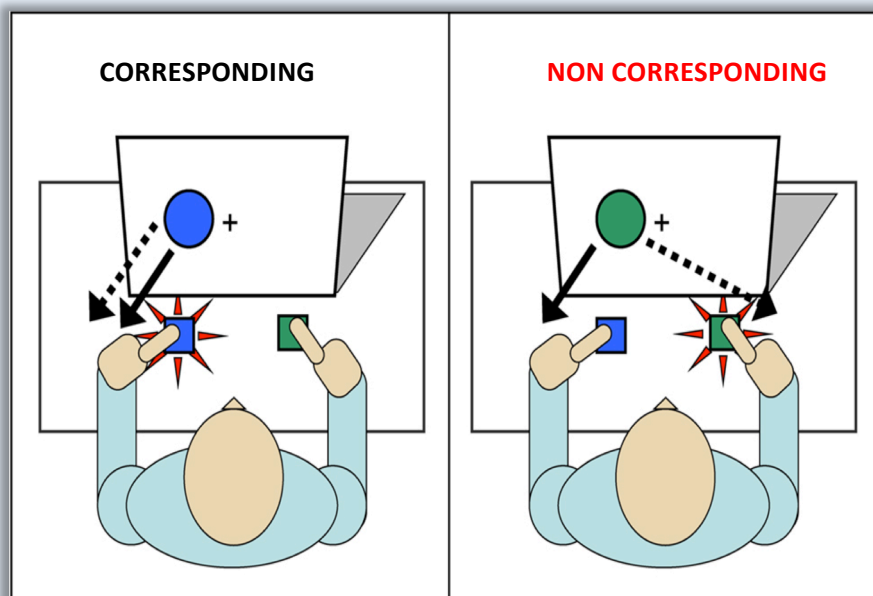
5.1 Introduction

The human ability to focus attention on relevant information and to neglect, at the same time, the irrelevant one, is a crucial issue in cognitive psychology. This ability is called cognitive control and is thought to originate from a dedicated cognitive mechanism that coordinates goal-driven behaviour (Norman & Shallice, 1986; Shiffrin & Schneider, 1977; Posner & Snyder, 1975; Broadbent, 1958). Cognitive control function is considered a high level process, which is commonly included in executive functions (EF), due also to its association with prefrontal cortex (PFC) activity (for a review see Miller, 2000). One of the functions of cognitive control is to adapt the cognitive system to different environmental situations (Kahneman, 1973) and this adaptation is usually driven by the detection of cognitive conflict (Botvinick et al., 2001), i.e. situation of interference between relevant and distracting stimuli. In cognitive psychology different conflict tasks were designed to study cognitive control: a common feature of these tasks is the presence of irrelevant information that slows down the processing of relevant information. In the Simon task (see box 1) left or right responses are associated with non-spatial stimulus features, whereas the stimulus is presented either on the left or the right side. Responses are faster and more accurate when stimulus and response location correspond, i.e. corresponding (C) trials, than when they do not correspond, i.e. non-corresponding (NC) trials. The difference between responses to C and NC trials is called Simon effect (Simon & Small, 1969). Despite this traditional structure of conflict task, it is generally recognized that cognitive control is involved not only in situation of cognitive interference and conflict, but it also “invoked” in emotional situations as danger (Norman & Shallice, 1986; Baddeley, 1972). Neuroimaging studies support this assumption: recent findings report that while the dorsolateral prefrontal cortex is a crucial region for the employment of cognitive control (Miller & Cohen,

2001) the anterior cingulate cortex is involved in signaling the need for the allocation of extra cognitive control (Botvinick et al., 2001). In detail, the anterior cingulate cortex is involved in the monitoring of cognitive conflict (Kim et al., 2013; Botvinick et al., 2001- 2004), but also responds to negative emotions, such as pain and negative feedbacks (Fomberstein et al., 2013; Santesso et al., 2012; Schakman et al., 2011; Botvinik, 2007).

Box 1: Simon task and Simon effect

In cognitive psychology, different laboratory tasks were developed with the aim to measure cognitive control capacity in humans. Common feature of these tasks is the induction of conflict between the processing of relevant and irrelevant information. In the Simon task (Simon & Rudell, 1967; Simon & Small, 1969) conflict is created by the automatic tendency to respond to the stimulus location, irrelevant dimension of stimulus target that interferes with the response to relevant information. The correspondence between stimulus location and response button creates two different conditions: corresponding and not corresponding.



Non-corresponding trials (right picture) make people slower and less accurate in comparison to corresponding conditions (left picture). The significant difference between the performances in these two conditions is named "**Simon Effect**" (Simon, 1969).

Moreover, sequential analyses have provided evidence for trial-to-trial adjustments: the Simon effect is function of stimulus–response correspondence in both the current trial and the previous trial. In detail the Simon effect is less pronounced, or even absent, if the previous trial is non-corresponding.

This phenomenon is known as "**conflict adaptation effect**" (Gratton et al., 1992).

On the basis of this assumption, many variants of the classical conflict tasks were proposed. A first variant introduced emotional stimuli creating “emotional conflict” situations with the aim of exploring the interaction between emotion processing and conflict resolution (Padmala et al., 2011; Egner et al., 2008; Etkin et al., 2006). Other variants, instead, introduced additional emotional variables during the execution of classical tasks, to evaluate if these variables might influence different aspects of conflict processing (Xue et al., 2013; Braem et al., 2012; van Steenbergen et al., 2012; Chiew et al., 2011; Sturmer et al., 2011; Kanske & Kotz, 2011a-b; 2010; Krebs et al., 2010). What links these studies is the objective of exploring the role of an emotional manipulation on cognitive control, trying to explore the interaction between emotional stimuli, positive or negative, and the recruitment of attentional resources. Despite an increasing interest in this research field, most of these studies have explored the effect of emotional stimuli in conflict tasks, neglecting the potential role of motivation. A consequent result is that the interaction between cognitive-control mechanisms and motivational variables is still not well understood (Braem, 2013). For these reasons we decided to investigate if, and how, different motivational contexts can modulate cognitive control. In detail, we created a new task in which two different performance contingent feedbacks were introduced as motivational incentives in a conflict task, with the goal to explore the role of these incentives in cognitive control. This new task was designed introducing performance-related rewards and punishments in a Simon task, to promote fast and accurate responses.

First aim of this research concerned investigating the interaction between motivation and cognitive control, exploring in detail this phenomenon using a specified analysis approach, i.e. the diffusion model analysis (Ratcliff, 1978). Our objective was to explore if, and how, motivational aspect can influence the management of cognitive resources, from perceptual to decisional aspects.

The second aim of this study was to investigate if, and how, the interaction between motivation and cognitive control changes during ageing. This second aim was motivated by shared knowledge about age-related decline of EF (see chapter II) and, moreover, was inspired by recent findings about age-related deficits in feedback processing and reward based-learning (Eppinger et al., 2011; Mell et al., 2009-2005; Dreher et al., 2008).

Finally, this new experimental paradigm was built also to investigate if, and how, the feedback processing deficits reported by medicated Parkinson's disease (PD) patients (Kapogiannis et al., 2011; Bodi et al., 2009; Kobayakawa et al., 2010; Frank et al., 2007-2004) can affect the interaction between motivation and cognitive control.

The choice to study this phenomenon in ageing and in PD patients was motivated by at least two reasons. First of all, the mentioned knowledge about neural mechanisms involved in the interaction between affect, i.e. motivational or emotional factors, and cognitive control. The neural network that supervises the interaction between affect and cognitive control is mediated in fact also by dopaminergic activity. Given its critical role in reward processing and in motivational control (for reviews see Bromberg-Martin et al., 2010; Schultz, 1997) it has been proposed that dopamine mediates the interface between motivational and cognitive control (Aarts et al, 2010).

In an overall view, if the anterior cingulate cortex and the dorsolateral prefrontal cortex may be involved in the detection and evaluation of cognitive demands and in the implementation of the cognitive control needed, the dopamine reward systems may play an important modulatory function in the regulation of this interaction.

Exploring healthy ageing and PD patients under medication, in this study we want to explore the interaction between motivation and cognitive control in two conditions in which the dopaminergic system go through significant changes: a decline in ageing, and dysfunction in PD patients under medication.

Lastly, proposing our task to healthy elderly and to medicated PD patients we will have important clinical information. Our paradigm was built to be also similar to those employed in cognitive rehabilitation settings. Cognitive rehabilitation programs, in fact, are based on the use of cognitive tasks in which the use of feedback is often recommended for the enhancement of motivation and for the improvement of the performance (Cicerone et al., 2011; Cappa et al., 2005). With our investigation we also want to explore the feasibility to use this kind of rehabilitation procedure in PD patients, a clinical condition in which general EF deficits (for a review see Dirnberger & Marjan, 2013; Kudlicka et al., 2011) and specific feedback-processing deficits (Kapogiannis et al., 2011; Bodi et al., 2009; Frank et al., 2007-2004) may compromise their rehabilitation itself.

5.2 Method

Participants

Fifty-seven participants were recruited for this study: twenty-seven young subjects (8 male, age range= 20-35 years, mean= 24.7, sd=3.4), fifteen old subjects (4 male; age range= 48-81 years; mean= 68.1 sd=9.6) and fifteen PD patients (6 male; age range= 49-85 years; mean= 71.8, sd=8.7) participated in the experiment after giving written informed consent. Young participants were recruited at the University of Padova, while both PD patients and old participants were recruited in the Rehabilitation division of the Hospital of Suzzara (Mantova-Italy). The PD patients fulfilled formal diagnostic criteria for PD according to the Unified Parkinson's Disease Rating Scale (UPDRS; Fahn & Elton, 1987; Goetz et al., 2003), had a mean disease duration of 5.1 years (range of onset 2–13 years, sd= 3.8) and a mean estimated motor sub score of 22.13 (range 8-39, sd=10.2) on the UPDRS. Patients were asked to continue taking their medication at the required time on the day of testing, and testing sessions, which comprised cognitive assessment and experimental task. Six patients received dopamine precursors (levodopa), four patients were receiving dopamine agonists, three received a monoamine oxidase inhibitor (MAOI), and two patients were taking a combination of levodopa and dopamine agonists. Old participants and PD patients groups were matched for age, gender and education (table 5.1).

TABLE 5.1 Means and standard deviations for demographical characteristics of the tested samples; tests concern the comparison between old subjects and PD patients.

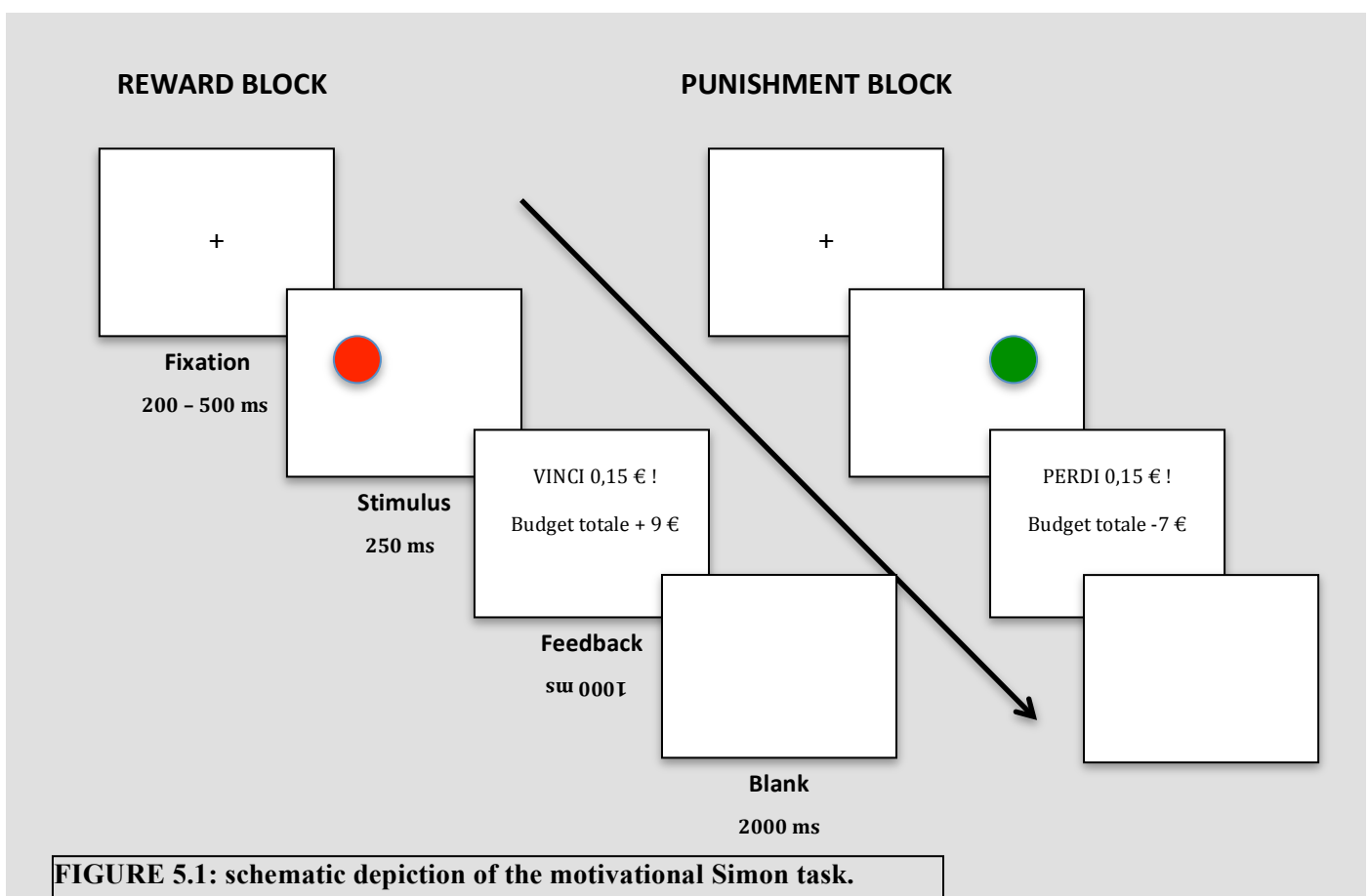
	Young N=27	Old N= 15	PD patients N= 15	Test (df)	p-value
Age (years)	24.7 ± 3.4	68.1 ± 9.6	71.8 ± 8.7	t ₍₂₈₎ =-1.07	ns
Gender	8 M	4 M	6 M	χ ² ₍₁₎ =.60	ns
Education (years)	17.1 ± 1.3	8.1 ± 3.5	8.4 ± 3.04	t ₍₂₈₎ =.223	ns

Exclusion/Inclusion criteria. Inclusion criteria for this study were participants with normal or corrected to normal vision. Exclusion criteria applied for the recruitment of young and old healthy participants were the presence of neurological disease (any medical conditions associated with a head injury, epilepsy, stroke), reported history of psychiatric disorder or neurological disease and use of psychiatric and neurological medications. Additionally, for both PD patients and old subjects exclusion criterion was a Mini Mental State Examination (MMSE; Folstein et al., 1975) score under the cut-off (24).

Measures

Motivational Simon Task. The experimental design of the new task employed in the present study is described in figure 5.1. The experiment ran with the E-Prime 2 software (Psychology Software Tools, Pittsburgh, PA) installed on a personal computer equipped with a 17" monitor. The structure of the experimental task respected a traditional Simon task: stimuli consisted of circles and squares, presented randomly to the right or left of a central fixation point, displayed with two possible colours, red or green, against a white background. Participants responded to the colour of the stimuli by pressing one of two horizontally aligned response buttons on a keyboard (A for green and L for red figures), using their left and right index fingers. Each trial started with the presentation of a central fixation cross for a random duration (from 200 to 500 ms), followed by the stimulus, presented for 250 ms. The session started with a practice block of 40 trials and with a following training block of 120 trials. After these two initial blocks in which no feedbacks were delivered, reward and punishment blocks followed, composed of 224 trials each, with one break after 123 trials. The presence of a short practice block has been designed to introduce the task before the recording of mean reaction times (RT) planned in the training block: the mean RT were calculated for C and NC trials, for the left and right responses separately. On the basis of the four means and standard deviations, for each participant four separate algorithms, for C and NC trials and each response, were calculated to identify the fastest responses that should be rewarded in the reward block [$RT < \text{mean RT of the training block} - (0.75 * sd)$], and the slowest responses that have to be punished in the punishment block [$RT > \text{mean RT training block} + (0.75 * sd)$].

With the use of these algorithms, in the reward block fast correct responses received a virtual bonus (+0.15 €), while in the punishment condition slow correct responses were penalized (-0.15 €). In both conditions, an acoustic feedback was given for errors; however, in the reward condition errors were not penalized, whereas in the punishment condition errors were punished like the slow responses (-0,15 €). After each feedback, the updated collected budget appeared at the bottom of the screen; at the end of experiment each participant had the information about their total virtual budget, as amount of total win and total loss. The order of reward and punishment blocks was counterbalanced across participants.



Neuropsychological assessment. Both old healthy subjects and PD patients were invited to attend a neuropsychological assessment session, after the initial screening with the MMSE. This session consisted of a short battery of standardised neuropsychological EF tests, and took no longer than one hour to complete.

In detail, phonemic fluency test and Trial Making Test A and B were selected from the battery Esame Neuropsicologico Breve-2 (ENB2, Mondini et al., 2011), to assess respectively set-switching, inhibition and response generation. The Frontal Assessment Battery (FAB; Dubois et al., 2000; see also Apollonio et al., 2005) was also administered, to have a global index of EF. Testing material is reported in Appendix.

Data analysis

Mean correct RT and accuracy rates were calculated in every group separately for each experimental block, reward and punishment. RT and accuracy data from the two blocks were also submitted to a diffusion model analysis (e.g., Ratcliff, 1978; Voss & Voss, 2008-2007; Spaniol et al., 2006) to obtain four parameters of interest (see box 2). This method optimizes the fit between empirical and predicted cumulative RT distributions using the Kolmogorov-Smirnov (KS) test statistic. We allowed $t\theta$, z , v and a parameters to vary with each of the two conditions (C and NC trials) and we estimated separate diffusion models for reward and punishment blocks, for each participant of the three groups. Mean correct RT, accuracy rates and each parameter of the diffusion model were separately analyzed with a 2x2x3 mixed ANOVA, including the within subject factors block (reward vs punishment) and correspondence (corresponding vs non corresponding), and the between subject factor group (young, old and patients). Post-hoc analyses were performed using Fisher test and applying Bonferroni correction for multiple comparisons.

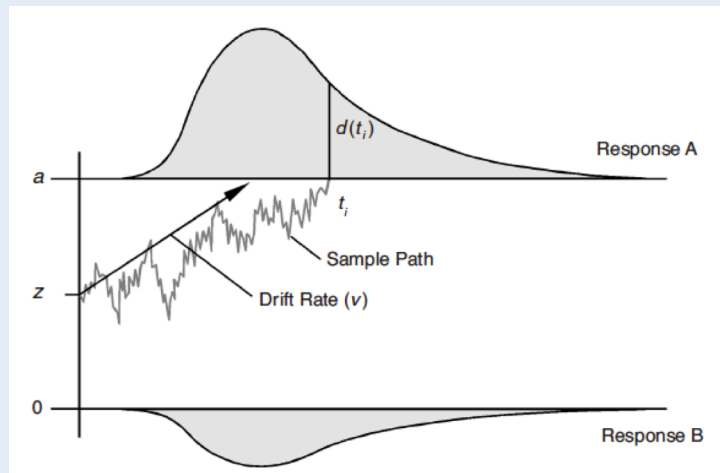
Diffusion model analysis

Model fit. We performed tests of fit separately for each diffusion model (i.e. for each participant and for each experimental block, resulting in a total of 114 models). As index of model fit, the fast dm method (Voss & Voss, 2008-2007) calculated a KS test for each model, where a significant result ($p < .05$) signalled model misfit. In this study the KS tests revealed significant result only for one young participant; therefore, the results presented here consider 26 young participants, 15 old and 15 PD patients.

Model parameters. Like raw RT and accuracy rates, every model parameter was analysed with a mixed ANOVA that included the within subject factors correspondence (C and NC) and block (reward and punishment), and the between subject factor group (young, old and PD patients).

Box 2: Diffusion model

During two-choice decisions, information accumulates until a response boundary is reached and the motor response is initiated. Assuming that, the diffusion model (Ratcliff, 1978) decomposes the performance into extra-decisional processes, perceptual and motor, and decisional processes.



Graphical illustration of diffusion process in a two choices decision tasks (from Voss et al., 2004).

Decisional processes

The model parameter a , known as **response boundary**, captures the distance between response thresholds and is interpreted as a measure of conservatism. In detail, **response boundary** is a measure of response caution or speed-accuracy trade-off (i.e., the distance between decision boundaries). With a larger response boundary, it takes longer for the decision process to reach its threshold, which decreases the probability of an erroneous response (Merkt et al., 2013).

Second decisional parameter is the represented by the **starting point (z)**, parameter that can map a priori biases in the decision thresholds. Since z parameter can only be interpreted in its relation to a parameter, it is preferable to report the relative starting point ($z_r = z/a$), because if z differs from $a/2$ (i.e., $z_r \neq 0.5$), different amounts of information are required before deciding on option A or B (Voss et al., 2013).

Extra-decisional processes

The model parameters v , the **drift rate**, indicates the relative amount of information per time unit that is needed; it can be interpreted as a measure of perceptual sensitivity in a between-person comparison while in a between-condition comparison is a measure of task difficulty (Voss et al., 2004).

The last parameter, t_0 , is defined as a measure of **non decisional time**, which consists of both motor and encoding processes that precede the decisional phase. This parameter value indicates the duration of all extra-decisional processes (Voss et al., 2004).

5.3 Results

Neuropsychological assessment

The neuropsychological data collected in old subjects and PD patients are reported in table 5.2. Even if, according to the exclusion criteria, every participant of both groups had a score over the cut-off (24), PD patients had a significantly lower mean score on MMSE than the control group. At a further examination of EF, PD patients showed lower scores in every neuropsychological test for EF. A lower number of words pronounced in the phonemic fluency test indicates a poorer response generation, while a greater difference between Trial making test A and B indicated declined set-switching ability. Finally, a lower performance on both the version of BPT suggested a declined ability to remember verbal material in condition of interference. Taken together these results indicate that our sample of PD patients had an overall compromised EF system, comparing with a control group matched for age, gender and education.

TABLE 5.2 Neuropsychological assessment. Mean scores and standard deviations of old subjects and PD patients' performance.

	Old N=15	PD patients N=15	t test (df)	p-value
MMSE	28.9 ± 1.4	27.06 ± 2.2	3.17 (23.6)	.004
Frontal Assessment Battery	16.9 ± 1.3	12.1 ± 3.1	5.46 (18.8)	.000
Phonemic fluency	9.9 ± 3.2	7.4 ± 2.4	2.45 (28)	.021
Trial Making test B-A	108.9 ± 64.1	195.7 ± 132.3	-2.15 (16)	.033
Brown Peterson task 10"	6.73 ± 1.9	4.53 ± 2.4	2.8 (29)	.009
Brown Peterson task 30"	7.1 ± 1.7	3.9 ± 1.9	4.87 (29)	.000

MMSE: Mini-Mental state examination; FAB: frontal assessment battery; BPT: Brown Peterson technique. In the phonemic fluency the score represents the mean number of words pronounced. Notes: in the TMT B-A scoring (TMT B execution time - TMT A execution time) 13 patients are considered because two patients were not able to do the B section of the test. In the phonemic fluency the score represents the mean number of words pronounced. Variations on df (degree of freedom) calculation are due to significant Levene test.

Motivational Simon Task

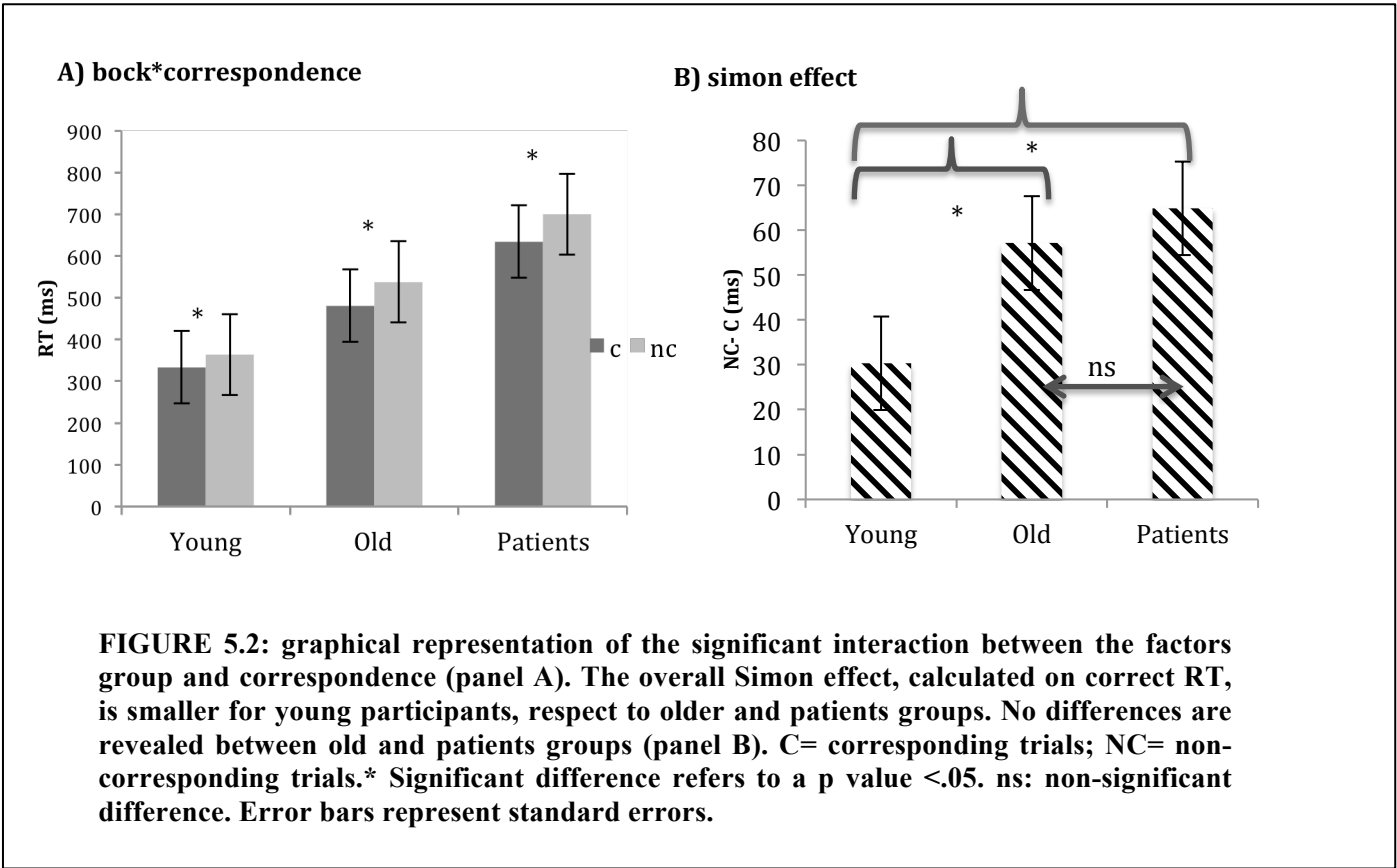
Performances of the three groups at the experimental tasks were reported in table 5.3: means and standard deviations for correct RT, accuracy rates and relative Simon effects, for each group and each experimental condition, were calculated.

TABLE 5.3 Means and standard deviations of correct RT and accuracy rates, with relative Simon effects.

Group	Block	Correspondence	Mean RT (ms)	Simon effect	Mean accuracy (%)	Simon effect
Young	Reward	C	324.1 ± 18.6	34.6	92 ± 5	-10
		NC	358.7 ± 17.8		82 ± 11	
	Punishment	C	342.7 ± 19.7	26.1	95 ± 3	-4
		NC	368.8 ± 19.8		91 ± 4	
Old	Reward	C	483.3 ± 24.2	62.3	96 ± 2	-10
		NC	545.6 ± 23.9		86 ± 7	
	Punishment	C	478.4 ± 26.5	51.9	96 ± 3	-7
		NC	530.3 ± 26.6		89 ± 6	
PD Patients	Reward	C	628.6 ± 24.2	65.7	91 ± 7	-5
		NC	694.3 ± 23.9		86 ± 10	
	Punishment	C	640.9 ± 26.5	64.02	92 ± 9	-6
		NC	704.9 ± 26.5		86 ± 12	

Notes: C: corresponding trial; NC: non-corresponding trial. Simon effect: (NC – C).

Reaction times. The rANOVA for correct RT yielded a main effect of correspondence [$F(1,54)=258.45$ $p<.001$ $n_p^2 = .827$], confirming the presence of an overall Simon effect. The main effect of group [$F(2,54)=55.44$ $p<.001$ $n_p^2 = .67$] indicated a significant slowing of RT going from young to old and PD patients. The significant group*correspondence interaction [$F(2,54)=13.08$; $p<.001$ $n_p^2 = .32$; see figure 15a] was explored with a post hoc analysis on Simon effect values. Results of this additional analysis revealed that young participants showed a smaller overall Simon effect, respect to older and patients group; no significant differences were found between old and patients (figure 5.2). The interaction between block and correspondence resulted as not significant [$F(2,54)=3.8$ $p=.056$ $n_p^2 = .06$].



Accuracy rates. The rANOVA for accuracy rates yielded significant main effects of correspondence [$F(1,54)=73.42$ $p<.001$ $n_p^2 = .57$], block [$F(1,54)=10.94$ $p<.005$ $n_p^2 = .17$], and the following significant interactions: block*correspondence [$F(1,54)=10.13$; $p<.005$ $n_p^2 = .16$] and block*group [$F(2,54)=5.99$; $p<.005$ $n_p^2 = .18$]. Fisher post hoc comparisons on the first interaction revealed an overall increased accuracy in NC trials of the punishment block; post hoc comparisons about the block*group interaction showed that only the young group modulated accuracy rates in relation to the block ($p<.05$), with a significant higher accuracy level in punishment condition (see figure 5.3a). The meaning of a three way interaction block*correspondence*group [$F(2,54)=4.53$; $p<.05$ $n_p^2 = .14$] was explored with a post hoc mixed ANOVA on Simon effect, with the factors block and group. Fisher post hoc comparisons, conducted to explore the significant interaction block*group [$F(2,54)=7.83$; $p<.005$ $n_p^2 = .22$], yielded by this additional ANOVA on the Simon effect, showed that only in the young group the magnitude of Simon effect was significantly modulated by the block, with greater Simon effect in the reward block ($p<.001$; see figure 5.3b).

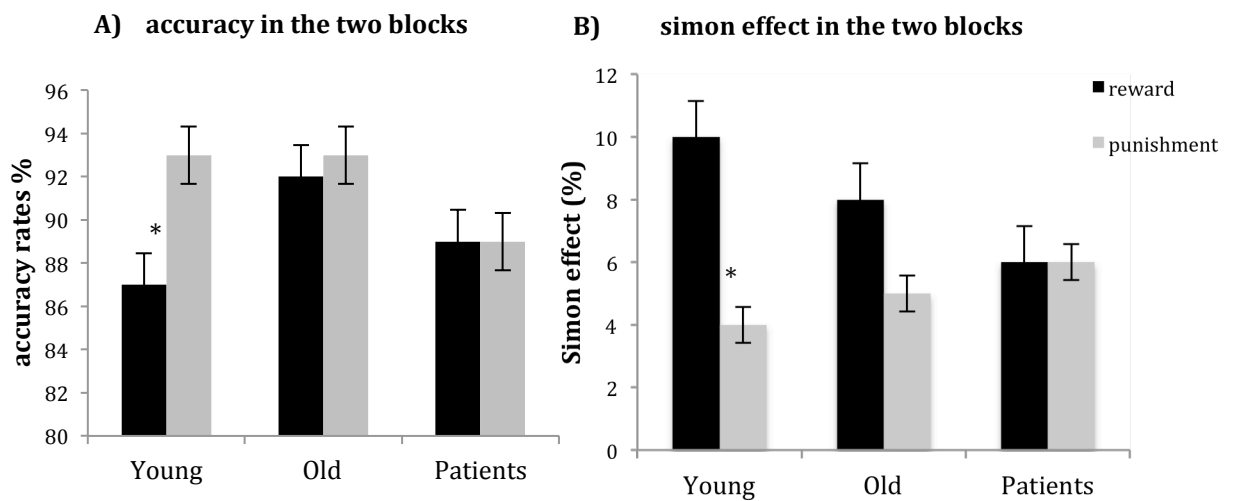


FIGURE 5.3: graphical representation of significant block*group. Panel A: young participants modulated accuracy levels depending from the block type. Panel B: young participants showed a greater Simon effect in the reward block. * Significant difference refers to a p value <.05. Error bars represent standard errors.

Boundary separation (a). A significant effect of correspondence [$F(1,53)= 36.4$; $p<.001$; $n_p^2 = .40$] showed that the overall decision process took longer to reach the threshold in C trial. The main effect of group [$F(2,53)= 20.4$; $p<.001$; $n_p^2 = .43$] indicated increasing a values in aging and in patients, given the significant differences between the three groups. The significant block*group interaction [$F(2,53)= 8.02$; $p<.005$; $n_p^2 = .23$] showed a different block modulation of a parameter in the three groups. Post hoc comparisons revealed that in young participants boundary separation, i.e. a parameter, increased in the punishment block, respect to the reward one. An opposite pattern was found in the old group (figure 5.4a) while no differences were found in PD patients, which showed absence of modulation of a parameter by the block. The significant block*correspondence* group interaction [$F(2,53)= 3.19$; $p<.05$; $n_p^2 = .10$], and post hoc comparisons, revealed these block depending modulation of a parameter, found in young and old groups, was driven by C trials responses. In C trials of the punishment block, young and older adults respectively showed higher and lower boundary separation, in comparison to C trials of the reward block.

Response bias (z/a). The main effect of block [$F(1,53)= 34.15$; $p<.001$; $n_p^2 = .39$] and the block*group interaction [$F(2,53)= 19.14$; $p<.001$; $n_p^2 = .41$] showed that young and older adults were significantly biased in favour of the correct response in the punishment block, while no difference was found in PD patients group (figure 5.4b). In addition, the main effect of group [$F(2,53)= 14.21$; $p<.001$; $n_p^2 = .34$] revealed that while response bias values were significantly higher in older adults ($z/a = .74$), compared to young ($z/a = .61$), patients showed significantly lower values ($z/a = .53$) respect to the older adults group.

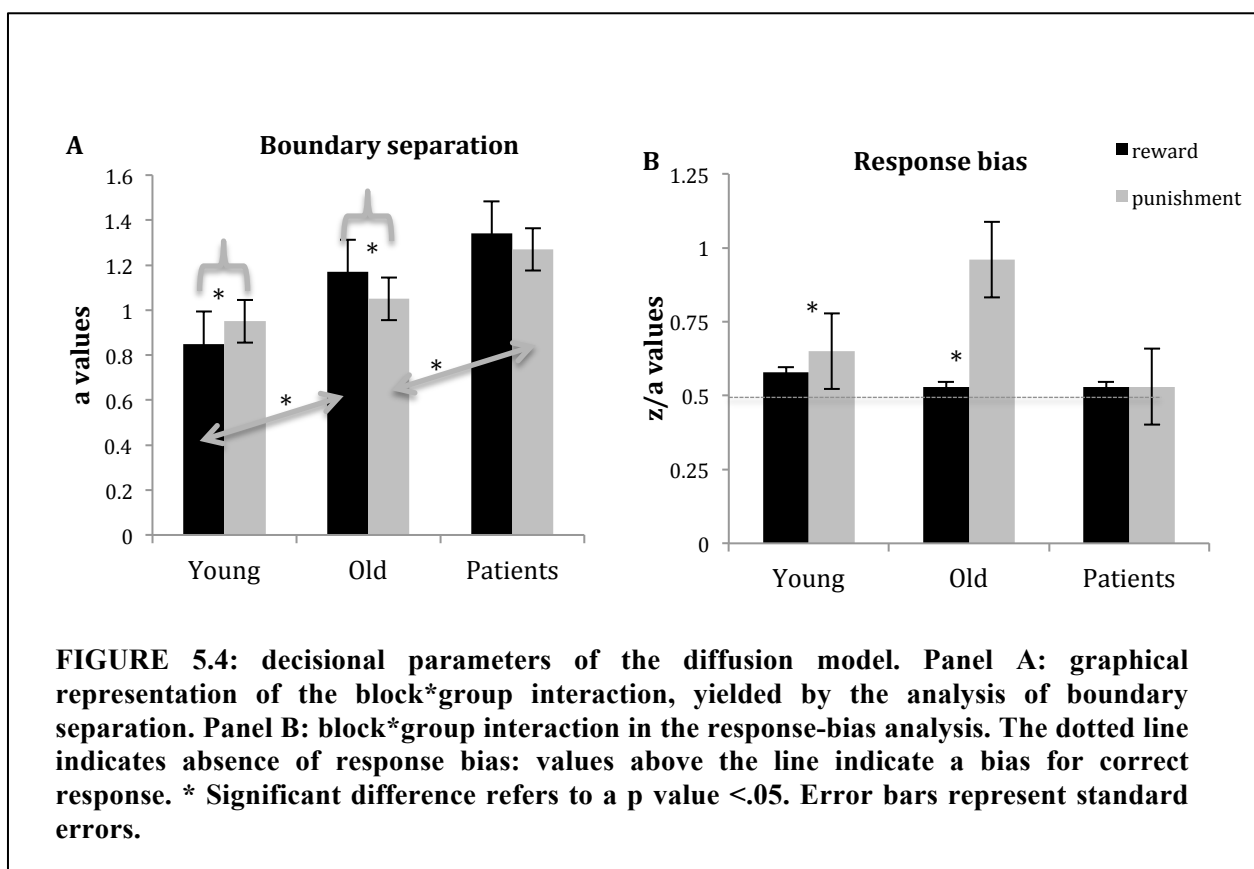


FIGURE 5.4: decisional parameters of the diffusion model. Panel A: graphical representation of the block*group interaction, yielded by the analysis of boundary separation. Panel B: block*group interaction in the response-bias analysis. The dotted line indicates absence of response bias: values above the line indicate a bias for correct response. * Significant difference refers to a p value <.05. Error bars represent standard errors.

Non-decision time (t_0). The main effect of group [$F(2,53)= 8.19$; $p<.005$; $n_p^2 = .23$] showed that the mean non-decision time was significantly higher for PD patients, respect to both young and older adults group ($p<.05$; Figure 5.5a).

Drift rate (v). A significant effect of block [$F(2,53)= 9.76$; $p<.005$; $n_p^2 = .15$] indicated that overall drift rate values were higher in the punishment block respect to the reward one.

The main effect of correspondence [$F(1,53)= 26.25$; $p<.001$; $\eta_p^2=.33$] showed as the drift rate was lower for non-corresponding than for corresponding trials. Finally the main effect of group [$F(2,53)= 22.75$; $p<.001$; $\eta_p^2 = .46$], and following post hoc comparison, revealed that PD patients showed significantly lower drift rate values, comparing with young and older adults groups (figure 5.5b; $p<.005$).

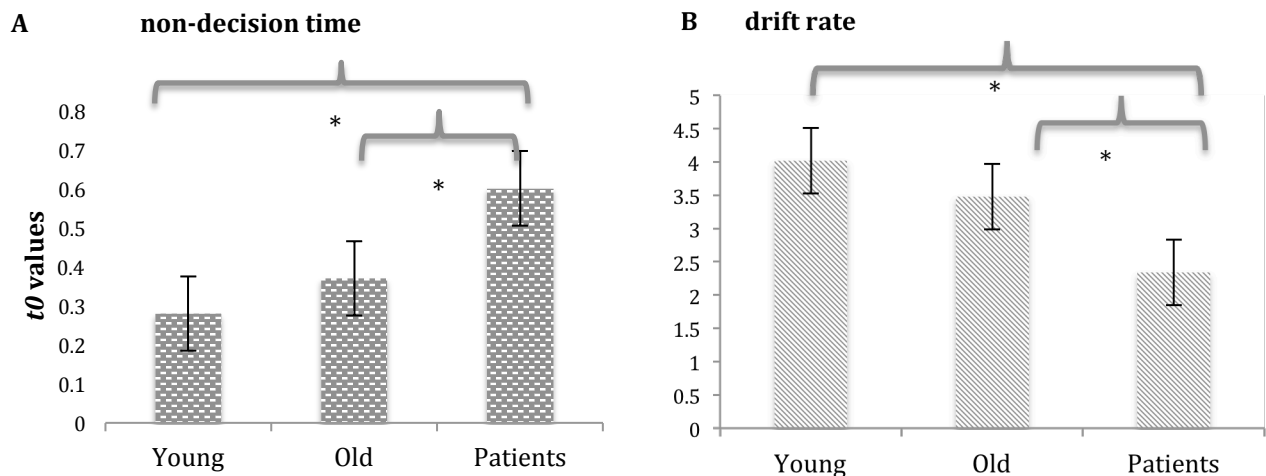


FIGURE 5.5: non-decisional model parameters. Panel A: non-decision time in the three groups. Panel B: drift rate in the three groups. * Significant difference refers to a p value <.05. Error bars represent standard errors.

5.4 Discussion and conclusion

The present study aimed at investigating if, and how, the presence of different motivational incentives can modulate the performance in a conflict task. Our goals were to explore the interaction between cognitive-control mechanisms and motivational variables employing a new paradigm, the “motivational Simon task”, and adopting a detailed analysis approach, the diffusion model analysis (Ratcliff, 1978). With the diffusion model analysis in fact we wanted to explore the detail of the interaction between motivation and cognitive control, to understand which components of the performance can be modulated by motivational incentives.

Important objective of this study was then to adopt this new task and the diffusion model analysis to explore if, and how, the interaction between motivation and cognitive control can change during ageing, and can be impaired in medicated PD patients. Before submitting data to the diffusion model analysis, RT and accuracy rates were evaluated. Results about RT performance first of all indicated that the motivational Simon task is a valid measure of cognitive control, yielding significant Simon effects in spite of the introduction of inter-trial stimuli, i.e. the feedbacks. Analysing group differences, RT data showed that in spite of the significant slowing, both older adults and PD patients manifested increased cost of conflict processing, showing a greater Simon effect respect to young, in line with previous findings (Paxton et al., 2008; Schmiedt-Fehr et al., 2006; Braver & Barch, 2002; Van der Lubbe & Verleger, 2002). Nevertheless, RT data did not show any effect of the motivational incentives in cognitive control measures.

A first index of interaction between motivation and cognitive control was showed however in the analysis of accuracy rates. Our results indicated that the young group modulated their performance in relation to the motivational incentive, with higher accuracy and smaller Simon effect when errors were penalized, i.e. in the punishment block. Old healthy subjects and medicated PD patients did not modulate overall accuracy and conflict processing in response to different motivational contexts.

Even if these first results indicated interesting difference between the three groups tested, it was with the diffusion model analysis, which combined RT and accuracy values, that we had more precise information.

First result of the diffusion model analysis concerned the decisional parameters. Results showed that the overall response style changed in the three groups, with an increasing “conservatory” approach going from young, to old and PD patients. Nevertheless, the old group showed the higher bias in favour of correct responses, while young participants and PD patients showed an almost absent bias. More importantly, young and old healthy participants modulated their response style and response bias depending on the block, which is supposed to induce different motivational status. These results indicated that PD patients did not show any difference depending on the block.

While in healthy condition the presence of motivational incentives impacts on the executive stages of information processing, in medicated PD patients this modulation seems to be absent.

Concurrently with these findings, the analysis of extra-decisional parameters added important information to understand this complex pattern.

Between group comparisons showed that old subjects did not spend more non-decision time respect to the younger. On the contrary, PD patients showed higher non-decision time comparing with both young and old subjects. Furthermore, while the performance of old and young subjects was comparable in terms of perceptual efficiency, PD patients showed a significantly slower information processing. In spite of these group difference, the analysis of these parameters showed as motivational incentives did not modulate the extra-decisional components of the performance, in none of the three groups.

Taken together, our results suggest that healthy people are able to modulate their performance depending on a motivational incentive, and that ageing do not affect this capacity, in line with previous works (Spaniol et al., 2011; Harsay et al., 2010). Even if adopting a different approach to the task respect to young people, old subjects show a preserved capacity to manage their resources in response to different motivational conditions. The different pattern of performance that we found between young and old participants is in line with literature about ageing differences in speed-accuracy balancing and decision-making: young generally perform quickly and are more accepting of errors, while old respond slowly trying to be more accurate (Starns & Ratcliff, 2010; Smith & Brewer, 1995; Hertzog et al., 1993; Baron & Matilla, 1989; Salthouse, 1979). What is important to highlight is that the capacity to modulate the performance in response to a motivational incentive is preserved in ageing, with an efficient modulation of the executive components of the performance, as what happens for young healthy people.

On the other hand, medicated PD patients without dementia, but with EF impairment, show an altered capacity to modulate the performance depending on motivational incentives. In this pathology, EF decline and also dopaminergic treatment could have worked together to create a complex pattern of dysfunctional performance. As briefly described above, the capacity to integrate motivation and cognitive control seems to be the result of a complex integration between EF, primarily sustained by the prefrontal cortex and anterior cingulate cortex activity, and the feedback processing capacity, in which the dopaminergic system has critical role. In PD, a dopaminergic dysregulation, subsequent to both aetiology and pharmacological treatment, can result in a generalised EF decline that affect goal-driven behaviour.

Even if our study can't address specific causal relations, EF and reward processing deficits (Kudlica et al., 2011; Kapogiannis et al., 2011; Bodi et al., 2009; Kobayakawa et al., 2010; Frank et al., 2007-2004) can be the reasons of the impaired motivational modulation of the performance showed by the results of the present study.

These final results have also important clinical implications. Investigating the interaction between motivation and cognitive control, results of the present study indicate that PD patients are unable to modulate their resources in response to performance-contingent feedbacks. In the light of the fact that in clinical neuropsychology most cognitive rehabilitation procedures are based on feedback-guided learning, where symbolic feedbacks, contingent upon performance, are used to motivate the performance of a patient, our study show a possible fallacy of that trend in this clinical condition. Feedback-based learning could be the wrong method to set a cognitive rehabilitation procedure if the subject of the therapy has EF deficits and, moreover, an altered feedback processing capacity.

In conclusion, our findings add information about mechanisms that underlie the function of motivational incentives in modulating the management of cognitive resources. In healthy condition, motivational incentives can modulate the decisional parameter of a performance and then the management of cognitive resources. On the contrary, when an EF decline compromise feedback processing capacity, the interaction between motivation and cognitive control can be inefficient.

CHAPTER VI - THIRD STUDY

EXECUTIVE FUNCTIONS AND DECISION MAKING: AN ERPs ANALYSIS OF FEEDBACK PROCESSING IN PARKINSON'S DISEASE

6.1 Introduction

A definition of the term “decision-making” could not be easy, because it represents one of the highest and most complex human abilities that is classically included in the EF “family”. According to Rogers (2011) we intend decision making as a complex process that “encompasses a range of functions through which motivational processes make contact with action selection mechanisms to express one behavioural output rather than any of the available alternatives”. This definition implicitly assumes that the decision process is based on the functions of selection and inhibition, working memory, planning, emotion, estimation and every process included in the term “executive control”.

Research about decision-making within cognitive neuroscience has largely increased over the last 20 years, starting from the study of patients with frontal lobe damage (Bechara et al., 1996-1994; Damasio, 1994), to the emergence of new disciplines as neuroeconomics (Glimcher et al., 2008). Even though this increasing interest has been accompanied by the development of divergent models, a consensus has been reached concerning some of the fundamental aspects of decision-making. From a cognitive psychology point of view, decision-making can be considered as the integration of three complementary abilities, summarized by Fang and colleagues (2009) which are: choice evaluation, response selection and feedback processing; in our opinion of these three abilities the last one has a crucial influence on the first two. In fact, before selecting or inhibiting an option, this should be evaluated and processed, and a correct connotation with positive or negative valence is possible only on the base of previous outcome evaluation experiences. The evaluation of our action outcomes and their anticipation appears then to be crucial for choice evaluation and for response selection, i.e for an efficient decision process. According to a more complete cognitive neuroscience point of view, it is shared knowledge that in normal decision-making an extended neural network is required, mainly comprising the prefrontal cortex (PFC) but including also the fronto-striatal and limbic loops, subcortical structures as basal ganglia, amygdala and anterior cingulate cortex (for a review see Gleichgerrcht et al., 2010; see figure 6.1).

Considering the important contribution of neurotransmitter systems in this network, it is possible to affirm that dopamine (DA) plays a key role in decision-making process (Rogers, 2011; Assadi et al., 2009). Despite its multi-faceted influence upon decision-making (Rogers, 2011), DA transmission has a crucial function in reward processing during reinforcement learning (Frank et al., 2004; Schultz, 2002) and the importance of the fronto-striatal system in learning and outcome monitoring is even more recognized (Hämmerer & Eppinger, 2012). Without going into details of the DA functioning in the reward circuit and in the decision-making network, there is considerable evidence for the idea that decline in dopaminergic neuromodulation affects outcome monitoring (Hämmerer & Eppinger, 2012) with possible result of an overall impairment in decision-making ability.

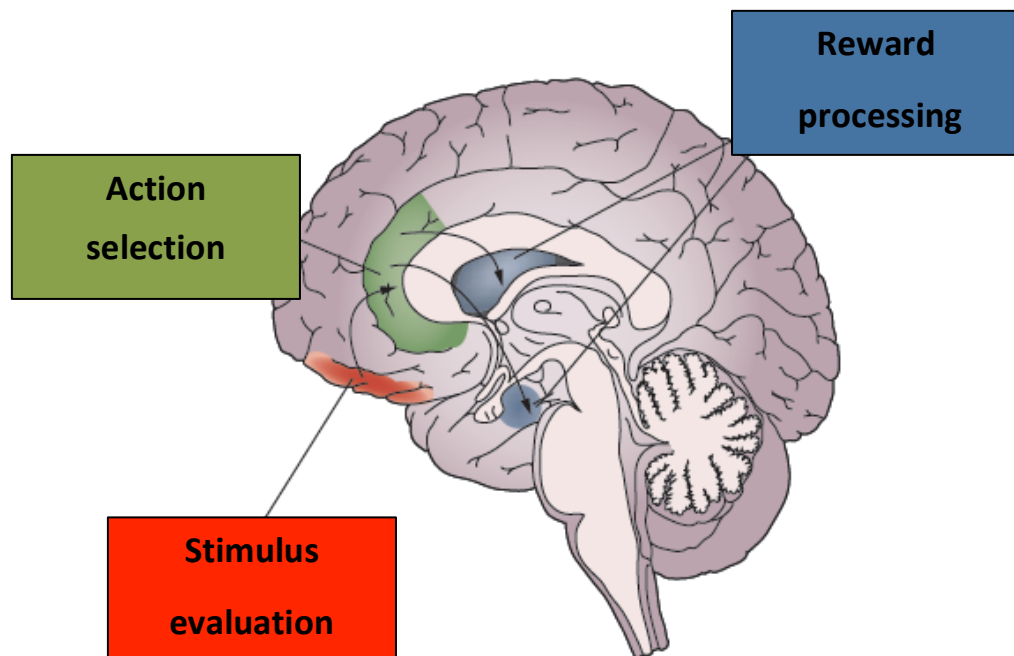


FIGURE 6.1. Simplified neuroanatomical model of decision-making (adapted from Gleichgerrcht et al., 2010). Three main systems are thought to be involved in decision-making capacity: stimulus encoding (orbitofrontal cortex- red), action selection (anterior cingulate cortex- green) and reward processing (basal ganglia and amygdala- blue). These regions work together with the PFC, parietal cortex and other subcortical structures as the insula.

Impaired decision-making abilities have been documented in many different clinical conditions, mainly in situations in which PFC was compromised. For example, evident decision-making impairment was firstly described in patients with frontal lobe damage (Fellows & Farah, 2005; Bechara et al., 1996-1997) or patients with fronto-temporal dementia (Torralva et al., 2009-2007; Rahman et al., 2005-1999), while interest in the decision-making capacity in healthy aging (Eppinger et al., 2011; Cauffman et al., 2010; Kovalchik et al., 2005; Finucane et al., 2002; MacPherson et al., 2002; Yates & Palatano, 1999) has also increased.

Parkinson's disease (PD) represents a clinical condition of particular interest in this research field because both aetiology and pharmacological therapies involve dopaminergic transmission and functionality of fronto-striatal system. More importantly, a growing recent literature is documenting the presence of feedback processing deficits in PD patients (Kapogiannis et al., 2011; Bodi et al., 2009; Kobayakawa et al., 2010; Frank et al., 2007-2004), concurrently with the development of cognitive and behavioural deficits linked to the impulse control disorder spectrum (for a review see Poletti & Bonuccelli, 2012). The application of one of the most common decision-making task, the Iowa Gambling Task (IGT; Bechara et al., 1994) in PD patients gave divergent results (Dirnberger & Jahanshahi, 2013, Poletti et al., 2011). Four studies with non-demented PD patients found non-significant impairments on the IGT (Poletti et al., 2010; Euteneuer et al., 2009; Thiel et al., 2003; Czernecki et al., 2002), whereas five studies showed that PD patients had a worse performance than healthy controls (Gescheidt et al., 2012; Kobayakawa et al., 2010-2008; Pagonabarraga et al., 2007; Mimura et al., 2006; Perretta et al., 2005). Three of these studies found non-significant effects of dopaminergic medication on the IGT performance in PD patients (Kobayakawa et al., 2010; Perretta et al., 2005; Czernecki et al., 2002;). Even if different decision-making tasks were used, findings are still divergent: patients with PD are impaired particularly when 'on' dopaminergic medication in the study of Euteneuer and colleagues (2009) or in the work of Cools and colleagues (2003), whereas PD patients without medication were impaired according to Brand (Brand et al., 2004). On the contrary Delazer and colleagues (2009) did not find any decision-making impairment in PD patients.

On the basis of these contrasting data, our goal is to add evidence in this field, by exploring in PD patients one of the crucial aspects of decision-making ability, i.e. the outcome evaluation, and trying to overcome limits and discrepancies of previous studies.

We employ once again the IGT (Bechara et al., 1994) that, without giving the knowledge about what the probabilities of certain outcomes are, represents a task that properly simulates the uncertainty of decision-making, typical of real life activities. Nevertheless, we chose a new approach: for the first time with PD patients, during the IGT execution we record the electroencephalogram activity. The goal of this study is in fact to evaluate the neural correlates of feedback processing using the Event Related Potential (ERPs; see box 3 for detail about this technique), with the aim of obtaining more information about underlying mechanisms of a possible impairment in decision-making. In detail, our objective is to explore the ERPs modulations related to the outcome of the decision, evaluating feedback-related negativity (FRN) and P3. These two ERPs components, in fact, are differentially modulated by the valence of an outcome and, for this reason, they are usually considered as electrophysiological markers of feedback processing. While FRN was shown to be sensitive to the valence of the feedback, with larger amplitude after negative than after positive feedback P3 is sensitive to both magnitude and valence of feedback with larger P3 after positive feedback than after negative (Ferdinand & Kray, 2013; Wu & Zhou, 2009; Hajcak et al., 2006; Holroyd et al., 2006; Toyomaki & Murohashi, 2005; Yeung & Sanfey, 2004; Gehring & Willoughby, 2002). Furthermore, while FRN reflects an early appraisal of feedback on a binary classification basis of good vs. bad outcomes, P3 seems to reflect a later, top-down controlled feedback evaluation process (Cui et al., 2013). As confirmed by a recent work by Cui and colleagues (2013), the recording of ERPs during the IGT represents a good method for the evaluation of these two electrophysiological markers of feedback processing, and for this reason we applied this methodology with PD patients. We predict that the results will be consistent with our previous study (see previous chapter) and we expect to find a difference in the electrophysiological patterns between PD patients and healthy control subjects.

Box 3: EVENT RELATED POTENTIALS (ERPs)

Event-Related potentials (ERPs) are small fluctuations in the electrical activity of the brain, which are related to a specific sensory, cognitive, or motor event (Luck, 2005). Recording electroencephalographic (EEG) activity during a time window that is time locked to the presentation of a stimulus, it is possible to record voltage changes, which are specifically linked to the brain's response to that stimulus (Coles & Rugg, 2002). These voltage changes reflect the summation of postsynaptic potentials and constitute the scalp recorded ERPs.

ERPs VOCABULARY

EPOCH: the defined time window, which is time locked to the occurrences of a particular event or stimulus during the EEG recording.

FILTERING: data-processing technique necessary to extract the ERP signal from the on-going EEG. Analogue or digital filters can be used at the time of recording and/or at the time of analysis, to attenuate activity outside the frequency of interest. In most cognitive experiments, the ERPs of interest are composed mostly of frequencies under about 30 Hz (Luck, 2005).

AVERAGING: signal-processing procedure necessary to extract the ERP signal from the on-going EEG. Averaging procedure is based on two fundamental assumptions: the neural activity related to the time-locking event is the same on every trial; only the EEG noise varies from trial to trial (Luck, 2005). Averaging involves the summation of a number of EEG epochs, considered the product of both the ERP and other voltage variations that are not time-locked to the event. On the assumption that EEG activity that is not time-locked to the event varies randomly across epochs, the background EEG averages to zero leaving a residual waveform that reflects the electrical activity that has a fixed temporal relationship to the event across epochs (Coles & Rugg, 2002; Fabiani et al., 2000).

WAVE: with the term wave or waveform it means a series of positive and negative voltage deflections, which result from the averaging process.

AMPLITUDE: this term indicates to the magnitude of the signal recorded, and is considered as the expression of the level of neural activation. ERPs amplitude is measured in micron volt (μV).

LATENCY: refers to the temporal dimension of the waveform recorded. ERPs latency is usually defined as the time from the stimulus onset and is measured in millisecond (ms).

PEAK: this term is used to indicate the most positive and negative deflections, in terms of amplitude, which characterise the ERPs wave. Peaks can be labelled according to their amplitude and latency. The letters *P* and *N* traditionally refer to the amplitude, designating positive-going and negative-going peaks respectively. Referring to their ordinal or temporal latency, letters *P* and *N* can be followed by a single digit (e.g. *N1*, *P3*), which refers to the peak's ordinal position within the waveform.

COMPONENT: ERPs components can be defined operationally as a part of the ERPs waveform with delineated scalp distribution and delineated relation to experimental variables (Otten & Rugg, 2005). Even if components are commonly labelled referring to their amplitude and latency within the waveform, as happens for the peak, the term component refers also to the sensory or cognitive process involved in the recorded ERPs activity. The amplitude of a component is commonly measured in one of two ways: as *peak amplitude*, measuring the amplitude at the peak latency, or as *mean amplitude*, computing the average amplitude over a time window that contains the component of interest. Because peak amplitude measures are particularly sensitive to noise in ERP waveforms, mean amplitude measures are preferable in situation of noise, for example in the comparisons between conditions with unequal number of trials, or in between groups comparisons, where the data from one group might be noisier than the data from the other one.

6.2 Method

Participants

Twenty-eight participants were recruited: fifteen (11 male) healthy subjects (age range 43-77 years; mean= 60.7 sd= 9.8) and thirteen (10 male) PD patients (age range 47-73 years; mean= 62.6 years, sd=8.3) participated in the study. Both PD patients and older adults were recruited in the Pederzoli Hospital, in Peschiera del Garda (Verona-Italy). The PD patients fulfilled formal diagnostic criteria for PD according to the Unified Parkinson's Disease Rating Scale (UPDRS; Fahn & Elton, 1987; Goetz et al., 2003), had mean disease duration of 4.9 years (range of onset 1–14 years, sd=3.4) and a mean estimated motor sub score of 8.8 (range 3-16, sd= 4) on the UPDRS. Patients were asked to continue taking their medication at the required time on the day of testing. Five patients received dopamine precursors (levodopa), two patients were receiving dopamine agonists, four received a monoamine oxidase inhibitor (MAOI), and two patients were taking a combination of levodopa and dopamine agonists. Healthy subjects and PD patients were matched for age, gender, education and MMSE score (see table 6.1) and for this reason the healthy subjects will be considered as control group. All participants gave signed informed consent after the purpose of the study and the protocol had been explained to them.

TABLE 6.1 Means and standard deviations of matched demographical characteristics and MMSE score in PD patients and control group.

	PD patients N= 13	Control group N= 15	Test (df)	p-value
Age (years)	62.6 ± 8.3	60.7 ± 9.8	t ₍₂₆₎ =.547	.ns
Gender	10 M	11 M	χ ² ₍₁₎ =1.19	.ns
Education (years)	8.7 ± 3.6	11.4 ± 4.3	t ₍₂₆₎ =-1.72	.ns
MMSE score	28.2 ± 1.3	27.86 ± 1.5	t ₍₂₆₎ =.666	.ns

MMSE: Mini Mental State Examination (Folstein et al., 1975)

Exclusion/Inclusion criteria. Inclusion criteria for this study were participants with normal or corrected to normal vision. Exclusion criteria applied in the recruitment of the control group were the presence of neurological disease (any medical conditions associated with a head injury, epilepsy, stroke), reported history of psychiatric disorder or neurological disease and use of psychiatric and neurological medications. Finally, for both patients and control group exclusion criterion was a Mini Mental State Examination (MMSE; Folstein et al., 1975) score under the cut-off (24).

Measures

Iowa Gambling Task. Decision-making was assessed using the Iowa Gambling Task (IGT; Bechara et al., 1994). This test was developed in the Iowa University to assess decision-making capacity in laboratory environment. Even if it was originally designed in analogical mode, in our study the IGT was implemented in a computerized version. The experiment ran with the E-Prime 2 software (Psychology Software Tools, Pittsburgh, PA) installed on a personal computer equipped with a 17" monitor.

The task consisted in the presentation, on a computer screen, of four decks named A, B, C and D. Each card in these decks can bring a win or a loss: participants were requested to gain as more as possible, choosing consecutively one card from any of the four decks, until the task shuts off automatically after 100 cards. The back of each deck looks the same, but they differ in composition. Decks A and B are considered disadvantageous, because they brought to big wins but also expensive losses, producing a net loss of 250€ in 10 cards. Deck C and D are considered advantageous decks because brought small wins, but smaller losses, causing a net gain of 250€ in block of 10 cards. The instructions given to the participants were the following: “ *in this screen you can see four decks, two are advantageous and two are disadvantageous. Each card of these decks can bring a win or a loss: the goal of this task is to win as much money as possible, and avoid losing money as much as possible, starting from a virtual budget of 2000 €.*” Participants did not know the number of choices and, moreover, which were the advantageous or the disadvantageous decks. Participants saw on the screen the amount of money that they won or loose; this amount was updated after each choice.

EEG recording. While participants performed the IGT, the electroencephalogram (EEG) was acquired from an array of 32 Ag/AgCl electrodes, through a Micromed electrode system. Electrodes were identified by brain hemisphere (odd numbers = left, even numbers = right) and general cortical zone (F = frontal, C = central, T = temporal, P = parietal, and O= occipital). 30 electrodes were mounted on an elastic cap, according to the International 10–20 system (Oostenveld & Praamstra, 2001; see figure 6.2).

Left and right mastoids served as reference, while the vertical and horizontal eye movements were recorded with two electro-oculogram (EOG) electrodes, placed below and at the outer canthus of the left eye. The ground electrode was located at POz channel (GND in the figure 1). Rating sample was 512 Hz, electrodes impedances were < 5 k Ω and a digital band-pass filter from 0.1 Hz to 30 Hz was applied off-line. Epochs were locked to feedback onset and were 2000 ms long, between 1000 ms before and 1000 ms after feedback onset.

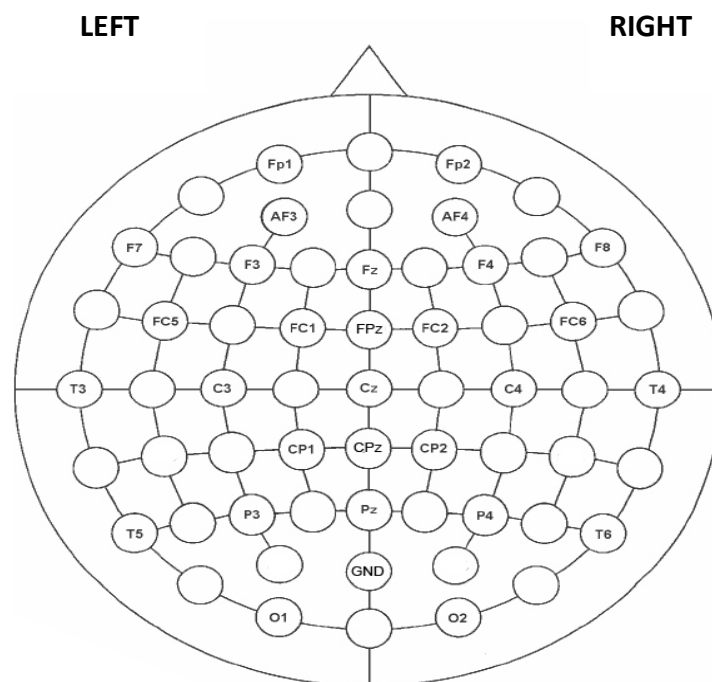


FIGURE 6.2: schematic representation of 30 electrodes scalp location (with labels) according to the International 10–20 system (Oostenveld and Praamstra, 2001); two electrodes were positioned at the left and the right mastoids, as reference, while two electrodes were placed below and at the outer canthus of the left eye, to record the electro-oculogram (EOG). GND corresponds to POz channel.

Dependent variables and data analysis

Behavioural variables. The IGT performance was evaluated using more than one parameters. The first analysis has been conducted exploring the modal value concerning decks choices. The preferential choice for each subject of the two groups was calculated, and the values were submitted to a Chi square frequency analysis, to evaluate if the distribution of choice frequencies was the same in the two groups. To obtain the IGT score, according to previous reports (Kobayakawa et al., 2010; Pagonabarraga et al., 2007; Fukui et al., 2005; Bechara et al., 1994) we subdivided the 100 selections into five blocks of 20 cards. For each block, the difference between the number of cards selected in advantageous decks (A and B) minus those chosen in disadvantageous ones (C and D) was calculated. In this way, five IGT scores were obtained for each participant, and the comparison between these values was considered as index of learning trend. In fact, increasing values of IGT score from the first to the last block indicate a preference for advantageous decks and the learning of the correct response strategy. Group differences were investigated submitting IGT scores to a mixed ANOVA, with the factors Group (patients and controls) and Time (from the first to the fifth block). Bonferroni correction for multiple comparisons was applied.

ERPs data. EEG data were processed using EEGLAB (Delorme & Makeig, 2004). Epochs were locked to the feedback presentation, and the averaging procedure was performed separately for positive and negative feedbacks. Artefacts correction was performed using independent components analysis technique (ICA; Makeig et al., 1996). The FRN was measured as the peak-to-peak difference between the positivity in the time window from 150 ms to 250 ms and the following negativity in a time window from 350 ms to 450 ms after feedback presentation. Since the FRN is usually most pronounced at fronto-central sites (Gehring & Willoughby, 2002) this measure was calculated at electrodes Fz, FCz and Cz and then submitted to a mixed ANOVA, with the factors Site (Fz, FCz and Cz), Feedback type (win vs loss) and Group (PD patients vs Control group). Mean amplitude of three time windows (150-250 ms; 250-350 ms; 350-450 ms) calculated at the midline electrodes Fz, Cz and Pz, were selected to measure P300 proportionally to FRN component.

These values were submitted to a mixed ANOVA, with the factors Interval (150-250 ms, 250-350 ms and 350-450 ms) Site (Fz, Cz, Pz), Feedback type (win vs loss) and Group (PD patients vs Control group). In both these ERPs analysis, Bonferroni correction for multiple comparisons was applied.

6.3 Results

Behavioural results. Exploring the modal values of deck choices, calculated for each subject of the two groups, results showed that the 70% of our patients preferred disadvantageous decks; only four patients (30%) preferred disadvantageous decks. On the contrary, the control group showed the opposite pattern: on 15 participants, the 80% preferred decks C and D, advantageous ones, while only 3 subject (20%) choose as preferential deck a disadvantageous (see figure 6.3a). The pattern of these choices was significantly different between patients and controls [$\chi^2_{(3)}=9.62$; $p<.05$].

Evaluating learning trend during the task, the ANOVA on the five IGT scores calculated in five blocks of 20 choices (IGT score= number of advantageous choices – number of disadvantageous choices), showed a main effect of Time [$F(4,104)=12.07$; $p<.001$ $n_p^2 = .317$], a main effect of Group [$F(1,26)=6.11$; $p<.05$ $n_p^2 = .19$] and a significant Time*Group interaction [$F(4,104)=4.09$; $p<.005$ $n_p^2 = .136$]. Post hoc analysis revealed within groups differences: while the control group showed significant differences between IGT scores, PD patients did not show any differences (see figure 6.3b). Furthermore the post-hoc analysis also revealed between groups differences: despite a better performance of PD patients in the first block ($p<0.05$), PD patients had a significantly lower IGT score, respect to the control group, in the third, fourth and fifth blocks ($p<0.05$; see figure 6.3c).

ERPs results. The feedback-locked ERPs of both groups are displayed in figure 6.4.

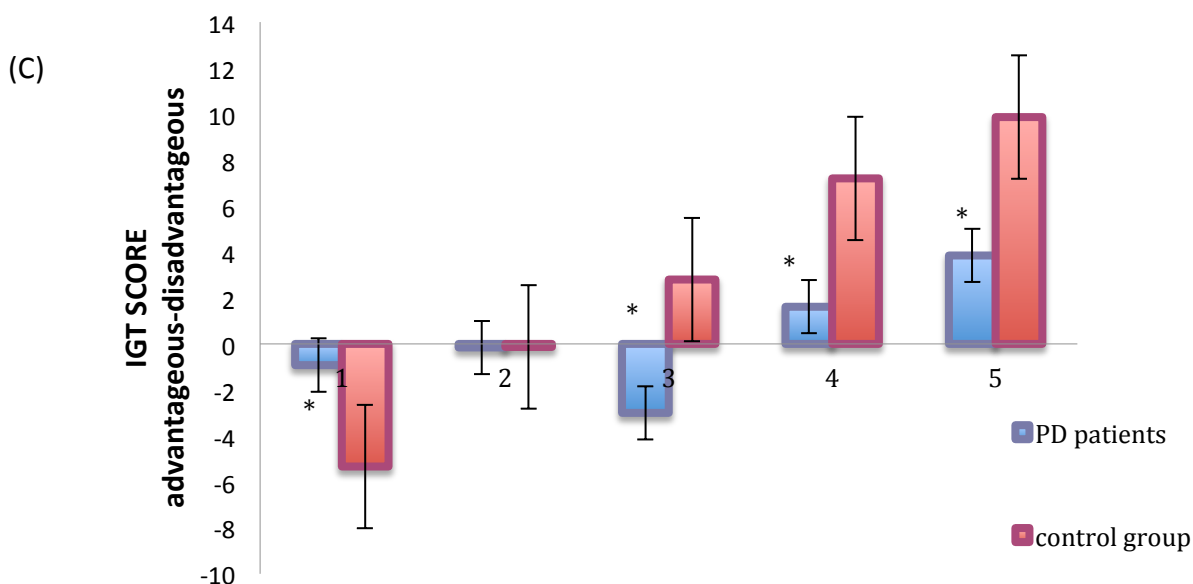
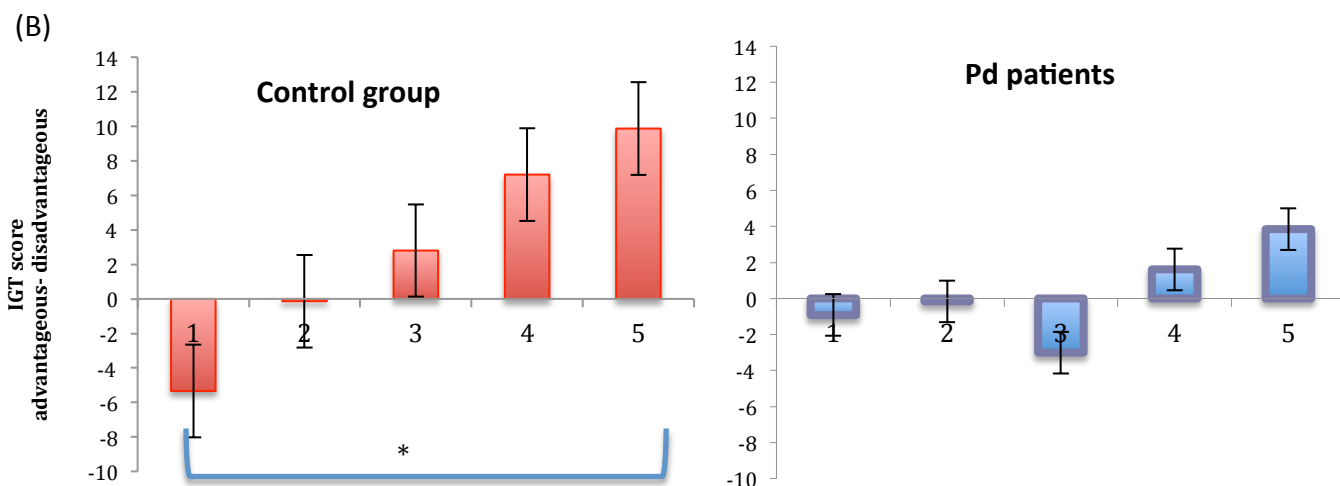
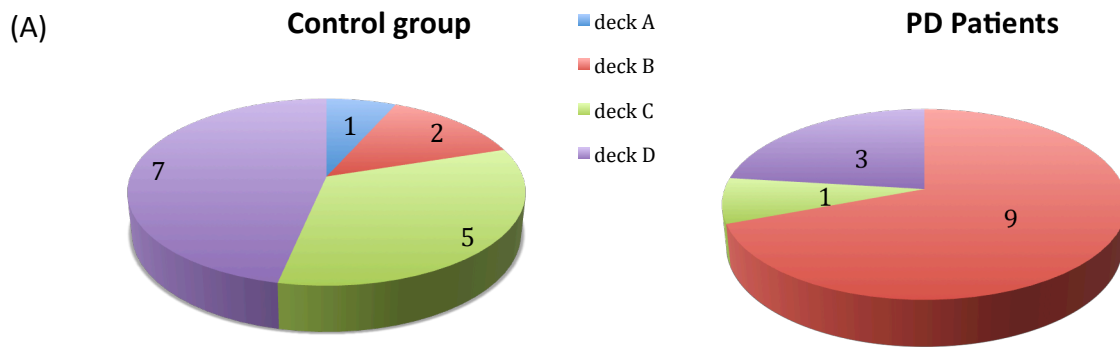


FIGURE 6.3: behavioural indices of performance at the Iowa Gambling task. Panel A: patterns of choice preference in the two groups; numbers represent the subjects who choose the deck. Panel B: learning trend in the two groups; Panel C: between groups comparison. * Significant difference refers to a p value <.05. Error bars represent standard errors.

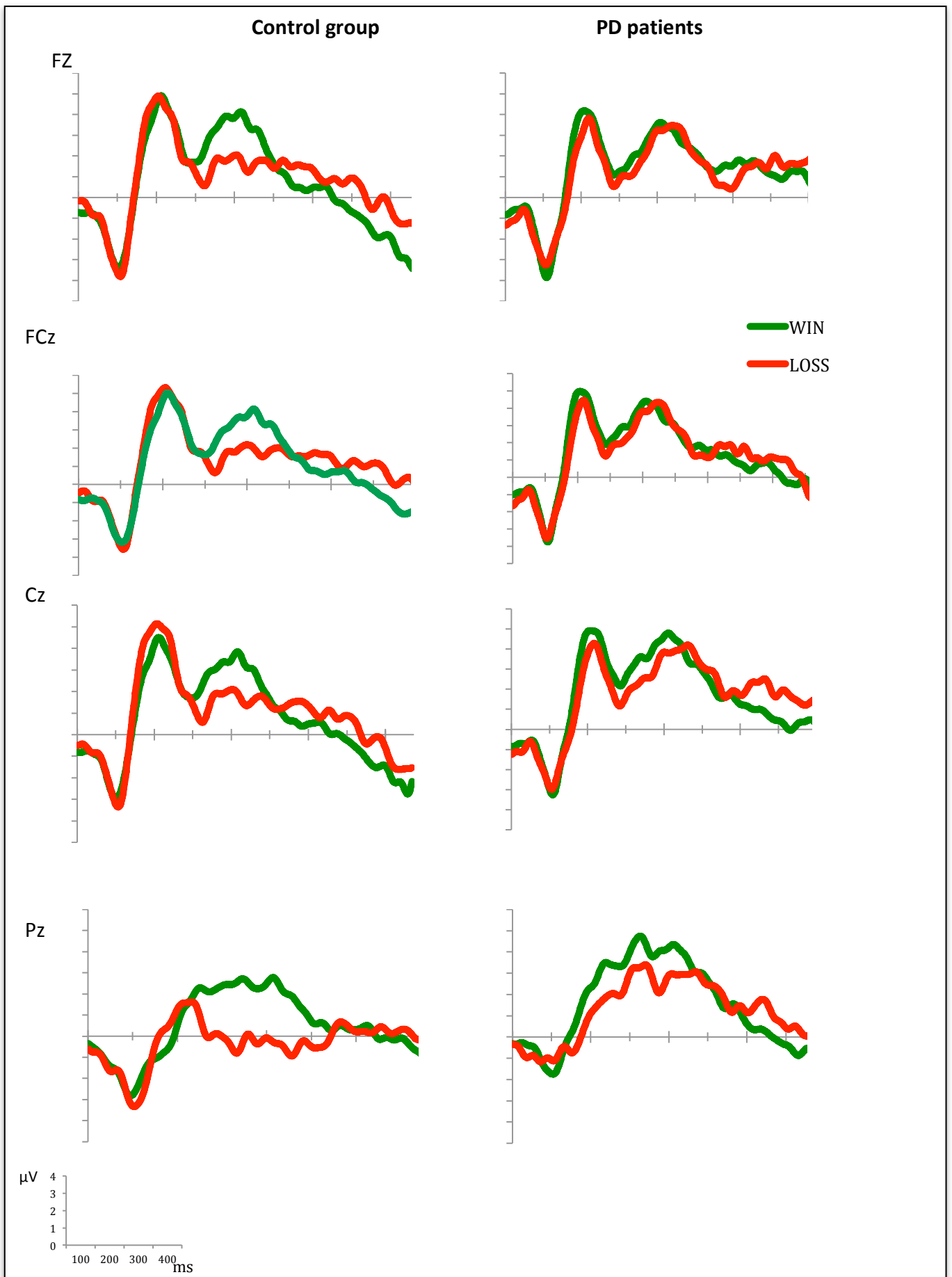


FIGURE 6.4: Grand average ERPs in the anterior (Fz, FCz) central (Cz) and parietal (Pz) sites.

FRN. The analysis on FRN recorded by Fz, FCz and Cz channels yielded a main effect of Feedback Type [$F(1,26) = 11.85, p < .005, \eta_p^2 = .31$] indicating that FRN was larger after a loss than after a win. Importantly, in spite of visual data inspection, we found no interaction between Group* Feedback Type.

P300. The analysis of the mean amplitude recorded in the three time intervals after feedback onset (150-250 ms, 250-350 ms and 350-450 ms) and at the midline electrodes Fz, Cz and Pz, showed main effects of Site [$F(2,52) = 3.30, p < .05, \eta_p^2 = .113$] and Feedback type [$F(1,26) = 7.71, p < .05, \eta_p^2 = .23$]: mean activity between 150 and 450 ms after feedback onset has higher amplitude at Cz (2.83 μV), comparing with Fz (2.39 μV) and Pz (1.80 μV). In addition, the ERPs amplitude was greater after positive feedbacks (2.84 μV) then negative ones (1.85 μV). The difference between positive and negative feedbacks was significant between 250 and 450 ms, as indicated by the Feedback*Time interaction [$F(2,52) = 5.14, p = .01, \eta_p^2 = .165$]. Site*Group interaction [$F(2,52) = 4.85, p < .05, \eta_p^2 = .156$] and subsequent post hoc comparisons, indicated that PD patients had a lower ($p < .005$) amplitude at frontal site (Fz) compared with central site (Cz), and a comparable amplitude at central (Cz) and parietal (Pz) sites. On the contrary, control group showed a significantly lower activity ($p < .05$) at the parietal site (Pz), comparing with central (Cz) and frontal (Fz) ones (see figure 6.5).

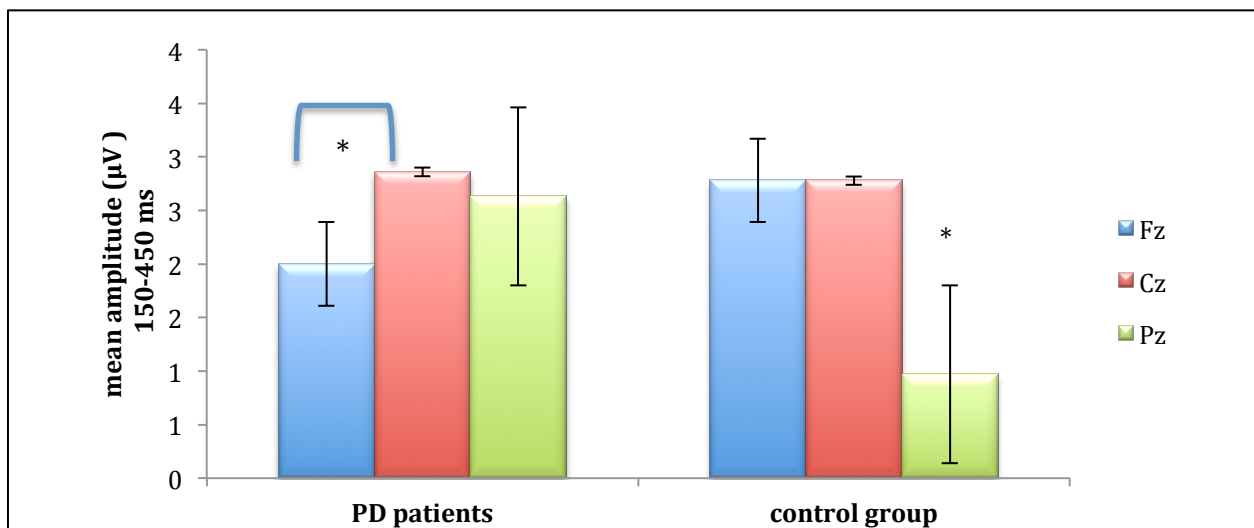


FIGURE 6.5: site*group significant interaction: PD patients had a lower ($p < .005$) amplitude at frontal site (Fz) compared with central site (Cz), showing no differences between central and parietal sites (Pz). On the contrary, control group showed a significantly lower activity ($p < .05$) at the parietal site (Pz), comparing with central and frontal ones. * Significant difference refers to a p value $< .05$. Error bars represent standard errors.

The Site*Feedback type interaction was also significant [$F(2,52) = 4.0, p < .05, \eta_p^2 = .133$], indicating significant differences between positive and negative feedback-evoked responses in Fz and Pz.

Finally, a significant interaction Feedback*Time*Group [$F(2,52) = 3.45, p < .05, \eta_p^2 = .117$] indicated that PD patients and control group presented different feedback-evoked responses. Post hoc comparisons specified that in the control group the mean amplitude, of both the time windows 250-350 ms and 350-450 ms, was significantly different after positive and negative feedbacks ($p < .05$). On the contrary, in PD patients non-significant differences between feedback-evoked responses were revealed (see figure 6.6).

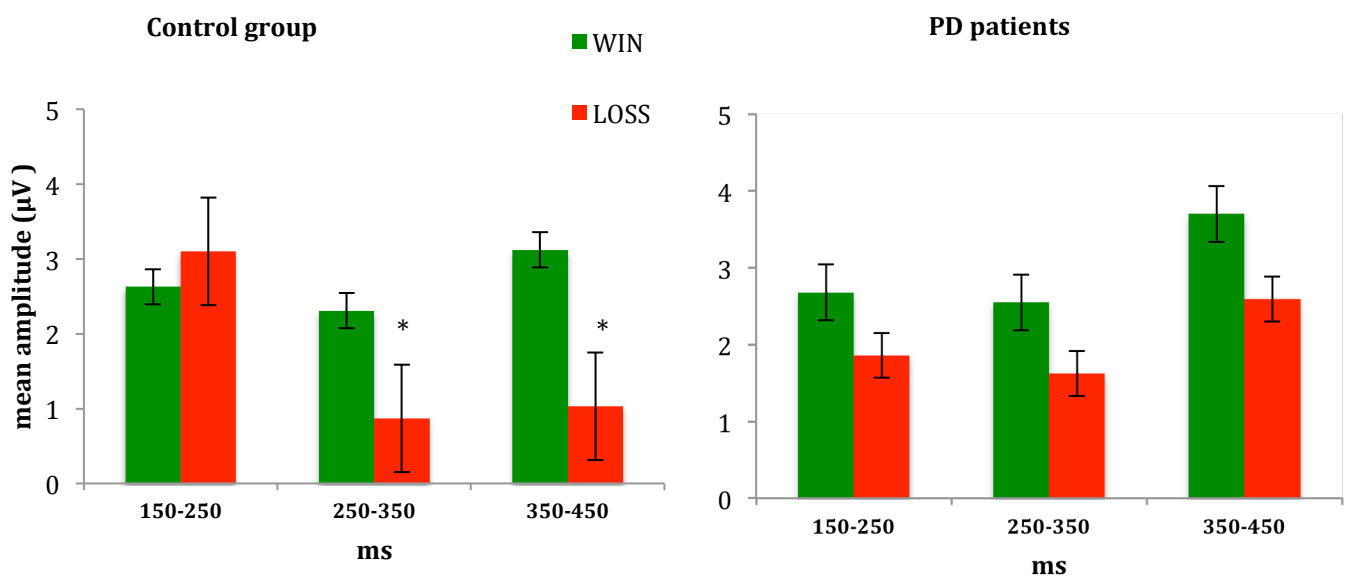


FIGURE 6.6: Feedback*Time*Group interaction: significant difference in the control group between win and loss evoked response, in both the time windows between 250-350 ms and 350-450 ms. No differences in PD patients group. * Significant difference refers to a p value <.05. Error bars represent standard errors.

6.4 Discussion and conclusion

In the current study we examined the neural correlates of feedback processing in a sample of PD patients, employing the ERPs technique during the IGT (Bechara et al., 1994), a task that simulates in a laboratory environment an uncertain decision-making situation. In detail, we explored the performance of a group of PD patients under dopaminergic treatment without cognitive impairment, analysing both behavioural and electrophysiological correlates of decision-making. Our aim was to add evidence in the exploration of cognitive and behavioural problems manifested in this clinical condition, especially in the light of a disagreeing literature background.

Our results indicate that medicated PD patients had a lower performance in the IGT (Bechara et al., 1994), compared to a matched control group. During the task PD patients showed a marked preference for disadvantageous choices. This kind of preference compromised the entire performance: even in the final phase of the task, PD patients continued to choose cards from the decks that had higher returns even if such choices were riskier, demonstrating a deficient capacity to learn and follow a successful strategy to improve their performance. These behavioural data support those previous studies that demonstrated an impaired performance of PD patients on the IGT (Gescheidt et al., 2012; Kobayakawa et al., 2010; Pagonabarraga et al., 2007; Perretta et al., 2005) but they do not add further information about possible reasons of this poor performance. With the aim to better explore the reason of this impairment, we recorded EEG activity during the task, evaluating in detail one of the abilities in the decision-making process, i.e. the feedback processing (Fang et al., 2009).

Analysing ERPs data in relation to feedback processing, FRN and P3 were evaluated in PD patients and in a group of matched healthy controls. Our results show no differences in FRN between PD patients and control group: all the subjects tested in this study manifested a comparable morphology for this component, with larger amplitude after a negative feedback, the loss, than after a positive feedback, the win.

Despite this absence of difference in FRN, when analysing the mean amplitude of the same time interval considered for its calculation, i.e. from 150 ms to 450 ms after feedback presentation, it emerged an interesting pattern of differences both within and between groups.

Even though no overall amplitude differences were found between the two groups, elderly healthy subjects showed a higher frontal and central activity in comparison to

the activity recorded by a parietal site; on the contrary, PD patients had a lower frontal activity, in comparison to the central and parietal ones. These differences in the shift of the signal distribution show an interesting finding: while our healthy elderly subjects showed a classical anterior-posterior asymmetry, a well-known finding in older adults and often interpreted in terms of compensatory resource allocation (Ferdinand & Kray, 2013; Daffner et al., 2011- 2006; Adrover-Roig & Barceló, 2010; Reuter-Lorenz & Lustig, 2005), our PD patients displayed a different recruitment of neural resources, with an opposite asymmetry. This could be interpreted as a failure of PD patients in this compensatory mechanism, probably due to a compromised PFC functioning. Furthermore, from the analysis of the mean amplitude in this time window, our results revealed a group difference in feedback related modulation of P3 component. In the control group the mean amplitude recorded between 250 and 450 ms after feedback onset was significantly modulated by the valence of the outcome, but in PD patients there were no differences between positive and negative feedback-evoked responses. This means that while older adults showed larger P3 amplitudes after positive than after negative feedback, PD patients displayed the same response after both feedbacks. This finding suggests that PD patients do not correctly discriminate the valence of an outcome and the fact that this absence of valence modulation manifests itself only in the later stage of the ERPs response, assumes a particular importance.

According to literature, the P3 is thought to reflect an evaluation process associated with working memory updating (Polich, 2007- 2004; Donchin & Coles, 1988) and the so called “positivity effect”, i.e. larger P3 amplitude after positive than after negative feedback, was supposed to reflect the evaluation of a positive feedback as more task relevant, because it signals that the intended goal has been achieved (Ferdinand & Kray, 2013; see also Bellebaum & Daum, 2008).

We agree in accepting FRN as an index of expectancy violations rather than an absolute valence classification (Alexander and Brown, 2011; Jessup et al., 2010; Oliveira et al., 2007; Holroyd et al., 2006) and in interpreting the P3 as a component sensitive to valence and relevance of feedback that reflects the context updating process and that contributes to performance monitoring evaluating the task-relevant feedback which can then contribute to behavioural adaptation (Ferdinand & Kray, 2013).

Considering the above statements, we can summarize our results with the following

conclusion: while an early appraisal of feedback appears to be preserved, a top-down controlled feedback evaluation process seems to be compromised in medicated PD patients. Their comparable response to positive and negative outcomes of a choice would reflect an altered capacity to discriminate and evaluate the task-relevant information, with resultant impairment in choice evaluation and action selection, i.e. a compromised decision-making ability.

As far as we know, there is no other research that has examined the feedback related ERPs patterns of PD patients in the IGT, and our results add important information to the understanding of the poorer performance of these patients in this task.

Taken together, our results are in line with the growing literature about feedback processing abnormalities in PD patients (Kapogiannis et al., 2011; Kobayakawa et al., 2010; Bodi et al., 2009; Frank et al., 2007-2004) and suggest that in PD patients an incorrect evaluation of context-relevant outcome could be the reason of a poor performance in this decision-making task, and may be one of the reasons for the development of cognitive and behavioural problems related to impulse control disorder.

CHAPTER VII

GENERAL DISCUSSION AND CONCLUSIONS

The goal of the present work was to investigate executive functions (EF) in ageing and in Parkinson's disease. In detail our aim was to investigate working memory (WM) and feedback processing in healthy elderly and in medicated Parkinson's disease (PD) patients, in order to explore two cognitive abilities related with the dopaminergic systems (Hämmerer & Eppinger, 2012; Bäckman et al., 2010-2006; Bäckman & Farde, 2005). In this way EF were explored in a condition of decreased dopaminergic functionality, i.e. in healthy ageing, and in a condition of possible dopaminergic "dysregulation", i.e. in medicated PD patients.

In the first study a new task was employed to evaluate the top down components of WM. More specifically we evaluated the capacities to focus the resources on task relevant information and to inhibit the irrelevant one, essential capacities for conflict resolution in WM. The task employed was designed as a "Stroop-like paradigm", where relevant and irrelevant information were combined in congruent or incongruent manner to create conflict situations, with the aim of inducing interference and facilitation effects. Age-related differences in WM were investigated applying the paradigm to three groups of healthy subjects: young, adults and old participants. On the other hand, the exploration of dopaminergic "dysregulation" effects in WM was possible applying the paradigm in a group of medicated PD patients, matched for age, gender and education with the healthy old participants. Our results showed lifespan differences in executive attention and inhibition components of WM. Healthy adults showed interference effect in their accuracy performance while, older adults showed facilitation effect in term of both latency and accuracy. These results confirmed the presence of an age-related decline in top down components of WM: the inhibitory control seems to be not perfectly efficient in adult and old subjects, as it is in younger people, when the information to inhibit is symbolic and not perceptual. In adults and old people, transient information stored in WM had detrimental effects on performance. Even if adults seemed to control their performance in terms of latency, both adult and older people were exposed to "capture errors" (Reason, 1990; Rasmussen, 1982), which were the most representative index of the failure to inhibit the irrelevant information.

This failure became evident through significant interference effects in adult, and through significant facilitation and interference effects in older people. The fact that facilitation and interference emerged differently during the lifespan could support the existence of two different mechanisms on the base of these effects (Lindsay & Jacoby, 1994), which could undergo independently to the age-related decline.

A group of medicated PD patients underwent the same experimental paradigm. PD patients tested in this study, which were under dopaminergic treatment and manifested a poorer performance in classical EF tests, showed a different pattern of performances in the experimental paradigm, respect to their control group. For what concerns accuracy rates, PD patients showed significant facilitation and interference effects and, moreover, they manifested an increased sensitivity to the irrelevant information, respect to the control group. PD patients in fact, even if with comparable overall accuracy, showed different accuracy rates depending on the congruence of the information stored in working memory, with significantly more errors in incongruent conditions. Despite that, PD patients did not show any significant effect of the irrelevant information in terms of latency. While the control group showed significant facilitation effects measured by response times, PD patients showed significant effects of the irrelevant information only in the accuracy. This pattern of results could be plausible in the light of the evidences about the role of dopaminergic medication on WM tasks (see Moustafa et al., 2008). Even if their accuracy was influenced by irrelevant information, PD patients seemed to be more able to control their performance in terms of latency.

In summary, the results of the first study highlighted the presence of age-related decline in top down components of WM, like executive attention and inhibitory control, in line with findings about age-related vulnerability to interference and decline in WM (Reuter-Lorenz & Sylvester, 2005). In addition, the results of this study showed as medicated PD patients performed like a control group in terms of accuracy, but better in terms of latency. Without comparing the performance of the same patients in an “off” condition, we cannot talk about the role of dopaminergic medication in this specific pattern of performance. However, our data are in line with previous findings about a double role of dopaminergic medications, which might lead to enhancements or impairments in WM tasks (Moustafa et al., 2008). Doing a speculation, in our PD patients the dopaminergic medication could have enhanced motor functions but, concurrently, could have impaired or, at least, could have not enhanced their ability to inhibit irrelevant information transiently encoded in WM.

In the second study, a different new task was employed to study feedback processing in healthy ageing and in PD. In detail, the performance of young and old healthy people, and of a group of medicated PD patients was explored in a conflict task, in which contingent feedbacks were introduced as motivational incentives. This second study had several objectives. First of all, we aimed at exploring the interaction between motivation and cognitive control, issue of interest in the recent literature. We wanted to add evidences in this field designing a new paradigm, the motivational Simon task, and analysing data with a specific method, i.e. the diffusion model analysis. With this analysis approach it was possible to evaluate which phase of the response was modulated by motivational variables, distinguish between decisional and extra-decisional components of our participants' performances. Secondly, we aimed at investigating if ageing effects on prefrontal cortex and on the dopaminergic functionality could affect the interaction between motivation and cognitive control. Following this second aim we applied the motivational Simon task in both, young and old healthy subjects. Final objective was to explore how a condition of dopaminergic "dysregulation" could affect the interaction between cognitive control and motivation. To reach this objective, a new group of medicated PD patients were tested with the motivational Simon task; their performance was compared with the group of old healthy subjects, matched for age, gender and education. With this last aim, we also referred to a clinical application of this exploration, i.e. the applicability of feedback-based learning paradigms for the cognitive rehabilitation of medicated PD patients.

Results of this second study fulfilled our objectives. Exploring the performance of healthy subjects with the diffusion model analysis we explored how, and in which dimensions, motivation can modulate cognitive control. Our results confirmed that the introduction of rewards and punishments in a conflict task is a useful method to explore how different motivation states, induced by these two different feedbacks, can lead to diverse approaches to the task. Our findings highlighted as a correct processing of different motivational incentives, positive or negative, permits to modulate the executive components of the response. Healthy people tested in our study were in fact able to adjust their performance in relation to different feedbacks and, therefore, different motivational states.

Young and old healthy subjects, even showing differences in their consideration of reward and punishment, were able to modulate their response strategy depending on the presence of positive and negative feedbacks, which differently incentivize a successful performance.

However, this capacity is impaired in PD. Analysing the performance of a group of medicated PD patients with EF impairment, it was possible to see that in this clinical condition the interaction between motivation and cognitive control is impaired. PD patients tested in this study did not modulate their performance in response to different feedback and, therefore, different motivational states. Unlike healthy subjects matched for age, gender and education, our PD patients showed the same performance in both the phases of the motivational Simon task, showing the inability to adapt their response strategy with the aim to obtain a successful performance. Taken together our results add information about how motivational incentives act in the modulation of cognitive resource management. Moreover, our results are in line with previous findings, which suggested a preserved feedback processing in ageing (Spaniol et al., 2011; Harsay et al., 2010) and an impaired feedback processing in medicated PD patients (Kapogiannis et al., 2011; Kobayakawa et al., 2010; Bodi et al., 2009; Frank et al., 2007-2004).

On the basis of the results of the second study, the third study presented in this thesis was aimed at exploring the electrophysiological correlates of feedback processing in medicated PD patients. In detail, we examined the ERPs components related to feedback processing in a new sample of medicated PD patients, recording the ERPs during the Iowa Gambling Task (IGT; Bechara et al., 1994). Confirming previous findings about an impaired performance of PD patients in this task, our results indicated that medicated PD patients had a lower performance on the IGT (Gescheidt et al., 2012; Kobayakawa et al., 2010; Pagonabarraga et al., 2007; Perretta et al., 2005). Furthermore, we also added important information about possible reasons of this lower performance.

The most important result of this third study is represented by the analysis of feedback modulation of the P3 component, i.e. a component sensitive to valence and relevance of feedbacks and that reflects context evaluation and performance monitoring (Ferdinand & Kray, 2013). In the control condition, which was represented by a group of old healthy subjects matched for age, gender and education with the PD patients, we found a positivity effect, i.e. a larger P3 amplitudes after positive than after negative feedback.

On the contrary, we did not find any positivity effect in our group of medicated PD patients. This result suggested that an impairment in top-down evaluation processes in medicated PD patients could be one of the reasons of feedback-processing deficits, which can bring to impaired choice evaluation and compromised decision-making ability.

Results of the third study are in line with the results of the second one, and they moreover agree with the previously mentioned literature about feedback processing abnormalities in medicated PD patients (Kapogiannis et al., 2011; Kobayakawa et al., 2010; Bodi et al., 2009; Frank et al., 2007-2004). The ERPs analysis of feedback processing suggested that in PD patients an incorrect evaluation of context-relevant outcome could be the reason of an impaired decision-making, and may be one of the reasons for the development of cognitive and behavioural problems related to impulse control disorder.

In conclusion, results of the present dissertation add information about how EF work, in the normal and in the pathological condition of PD. In the three works reported, EF were studied employing known and new experimental paradigms, with the aim to explore some detailed mechanisms never examined before, and to investigate other EF components that were previously explored with different, and sometimes inappropriate, evaluation methods. Using the terminology of Zelazo & Cunningham (2007), results of the present dissertation improve in detail the knowledge about “cool” components of EF, i.e. the WM and inhibitory control, and “hot” EF components, i.e. feedback processing and decision-making. Furthermore, the three studies reported proposed also an investigation of these components in normal ageing and in PD, basing on the association between the dopaminergic functionality and these specific EF (Hämmerer & Eppinger, 2012; Bäckman et al., 2010-2006; Bäckman & Farde, 2005).

Exploring these functions in different age classes, we confirm that “cool” components of EF, as WM and inhibitory control, are subject to a decline in normal ageing; however, we also show that “hot” EF, as feedback processing and decision-making, seem to be less affected by ageing. As reported in the first section of this dissertation, the actual question about ageing and EF concerns the exploration of which are the age-related deficits in executive control (Verhaeghen, 2011). Our results answer this question suggesting the presence of differential age-related declines of EF subcomponents, according to the hypothesis of West (2000).

At the same time, results of the present dissertation also show that medicated PD patients are impaired in feedback processing and decision-making, while they show a partial impairment in WM and inhibitory control. These results are in line with the suggestion of a complex dopaminergic “dysregulation” in medicated PD patients, suggesting further exploration of the role of pharmacological treatment in the expression of these EF deficits. Moreover, our findings could have important implication in clinical practice. Manifesting cognitive and behavioural deficits, PD patients can be subjects of cognitive and behavioural rehabilitation programs, which are often based on feedback-based learning procedures. To our opinion, a preliminary consideration of feedback processing ability in medicated PD patients would be appropriate in the rehabilitation setting, to evaluate feasibility and predict efficacy of those rehabilitation procedures. If medicated patients manifest a primary impairment in the outcome evaluation, every procedure centred on feedback-based learning would be inappropriate and ineffective.

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APPENDIX

UPDRS scale

Sezione I ATTI VITA' PSICHICA, COMPORTAMENTO E TONO DELL' UMORE

Alterazione delle facoltà intellettuali

0. Nessuna.
1. Lieve dimenticanza consistente in ricordo parziale di accadimenti, senza altre difficoltà.
2. Modesta perdita di memoria, con disorientamento e moderata difficoltà a trattare problemi complessi. Lieve ma moderato peggioramento delle funzioni domestiche con necessità di suggerimento occasionale.
3. Perdita di memoria severa con disorientamento nel tempo e spesso nello spazio. Peggioramento severo a trattare problemi.
4. Perdita di memoria severa con orientamento conservato solo alla persona. Incapacità ad emettere giudizi o a risolvere problemi. Richiede molto aiuto nella cura della persona. Non può essere lasciato da solo.

Alterazioni del pensiero

0. Nessuna.
1. Immaginazione fervida.
2. Allucinazioni "benigne" con interiorizzazione.
3. Allucinazioni o delusioni da occasionali a frequenti; senza interiorizzazione, possibile interferenza col quotidiano.
4. Allucinazioni permanenti, delusione o psicosi floride. Non in grado di badare a sé stessi.

Depressione

0. Assente.
1. Periodi di tristezza odii senso di colpa maggiori del normale, non sostenuto mai per giorni o settimane.
2. Depressione sostenuta (i settimana o più).
3. Depressione sostenuta con sintomi vegetativi (insonnia, anoressia, calo ponderale, caduta dell'interesse).
4. Depressione sostenuta con sintomi vegetativi e pensieri o tentativi suicidi.

Motivazione/iniziativa

0. Normale.
1. Meno affermativa del normale.
2. Perdita dell'iniziativa o disinteresse in attività elettive (non routinarie).
3. Perdita dell'iniziativa o disinteresse nel quotidiano (routine).
4. Isolamento, completa perdita della motivazione.

Sezione II ATTIVITÀ DI VITA QUOTIDIANA (DETERMINARE PER FASI ON/OFF)

Linguaggio

0. Normale.
1. Lievemente interessato; nessuna difficoltà ad essere compreso.

2. Moderatamente interessato; qualche volta richiesta la ripetizione delle affermazioni.
3. Severamente interessato; frequentemente richiesta la ripetizione delle affermazioni.
4. Incomprensibile per la maggior parte del tempo.

Salivazione

0. Normale.
1. Lieve ma definito eccesso di saliva nella bocca; può presentare sbavamento notturno.
2. Saliva moderatamente in eccesso; può presentare sbavamento minimo.
3. Marcato eccesso di saliva con qualche sbavamento.
4. Marcato sbavamento, richiede costante ripulimento.

Deglutizione

0. Normale.
1. Soffocamento raro.
2. Soffocamento occasionale.
3. Richiede cibi delicati.
4. Richiede alimentazione attraverso sondino nasogastrico o gastrostomia.

Scrittura

0. Normale.
1. Leggermente lenta o piccola.
2. Moderatamente lenta o piccola; tutte le parole sono leggibili.
3. Gravemente colpita; non tutte le parole sono leggibili.
4. La maggior parte delle parole non sono leggibili.

Taglio dei cibi e manualità degli utensili

0. Normale.
1. Piuttosto lento e goffo, ma non necessita di aiuto.
2. Può tagliare la maggior parte dei cibi, anche se goffamente e lentamente; necessita di qualche aiuto.
3. I cibi devono essere tagliati da qualcuno. ma può ancora alimentarsi lentamente.
4. Necessità di essere alimentati.

Il vestirsi

0. Normale.
1. Piuttosto lento, ma non necessita di aiuto.
2. Assistenza occasionale nell'abbottonamento e nell'infilare le braccia nelle maniche.
3. Richiesto aiuto considerevole, ma può compiere qualche movimento da solo.
4. Incapacità.

Igiene personale

0. Normale.
1. Piuttosto lenta, ma non necessita di aiuto.
2. Necessita di aiuto per la doccia o il bagno; molto lenta l'igiene personale.
3. Assistenza richiesta per le operazioni di lavaggio: usare lo spazzolino per i denti, asciugatura dei capelli, andare in bagno.
4. Cateteri di Foley o altri supporti meccanici.

Girarsi nel letto o aggiustarsi le coperte

0. Normale.
1. Piuttosto lento e goffo, ma non necessita di aiuto.
2. Può girarsi da solo o aggiustarsi le coperte, ma con

grande difficoltà.

3. Può tentare, ma non girarsi o aggiustarsi le coperte da solo.
4. Incapacità.

Caduta (non collegata a freezing)

0. Nessuna.
1. Cadute rare.
2. Cadute occasionali, meno di una al giorno.
3. Cadute, in media una al giorno.
4. Cadute, molte più di una al giorno.

Freezing durante la marcia

0. Nessuna.
1. Freezing raro durante la marcia; può avere avvio esitante.
2. Freezing occasionale durante la marcia.
3. Freezing frequente; occasionalmente caduta per freezing.
4. Cadute frequenti per freezing.

Marcia

0. Normale.
1. Leggera difficoltà; può non oscillare le braccia o può trascinare le gambe. -
2. Difficoltà moderata, ma richiede poca o nessuna assistenza.
3. Grave disturbo del moto, richiede assistenza.
4. Non può completamente camminare, anche con assistenza.

Tremore

0. Assente.
1. Fine ed infrequentemente presente.
2. Moderato; fastidioso per il paziente.
3. Severo; interferisce con molte attività.
4. Marcato; interferisce con la maggior parte delle attività.

Disturbi sensoriali collegati ai parkinsonismi

0. Nessuno.
1. Occasionalmente presenta intorpidimento, formicolio o lieve dolore.
2. Frequentemente presenta intorpidimento, formicolio o dolore; non angosciato.
3. Frequente sensazione dolorosa.
4. Dolore straziante.

Sezione III

ESAME DELLA MOTRICITÀ

Linguaggio

0. Normale.
1. Lieve perdita dell'espressione, della dizione e/o del volume.
2. Monotono. disarticolato ma comprensibile; moderatamente peggiorato.
3. Marcato peggioramento, difficoltà a comprendere.
4. Incomprensibile.

Espressione del volto

0. Normale.

1. Ipomimia minimale, potrebbe essere normale amimia.
2. Lieve ma definita diminuzione dell'espressione facciale.
3. Moderata ipomimia; labbra dischiuse per buona parte del tempo.
4. Volto immobile a maschera, con severa o completa perdita dell'espressività del volto; labbra dischiuse poco o molto.

Tremore a riposo

0. Assente.
1. Fine ed infrequentemente presente.
2. Leggero nell'ampiezza e persistente. Oppure moderato nell'ampiezza ma solo intermittenemente presente.
3. Moderato nell'ampiezza e presente per la maggior parte del tempo.
4. Marcato nell'ampiezza e presente per la maggior parte del tempo.

Attività o tremore posturale delle mani

0. Assente.
1. Fine; presente con l'attività.
2. Moderato nell'ampiezza, presente con l'attività.
3. Marcato, ma l'intero range dei movimenti si compie con facilità.
4. Severo, il range dei movimenti si compie con difficoltà.

Rigidità (valutata sui movimenti passivi delle articolazioni maggiori a paziente rilassato in posizione seduta. Ignorare i movimenti a scatti)

0. Assente.
1. Leggera o identificabile solo quando attivata allo specchio o da altri movimenti.
2. Da lieve a moderata.
3. Marcata, ma range completo di motricità compiuto facilmente.
4. Severa, range di motricità compiuto con difficoltà.

Picchiettamento delle dita (il paziente picchietta il pollice contro il dito indice in rapida successione con la massima ampiezza possibile, separatamente per ciascuna mano)

0. Normale.
1. Leggermente rallentato e/o ridotta l'ampiezza.
2. Moderatamente indebolito. Determinato e rapidamente faticoso. Può presentare arresto occasionale del movimento.
3. Severamente indebolito. Frequente esitazione nell'iniziare il movimento oppure arresto del movimento in corso.
4. Può a malapena eseguire il compito.

Movimento delle mani (il paziente apre e chiude le mani in rapida successione con la massima ampiezza possibile, separatamente per ciascuna mano)

0. Normale.
1. Leggermente rallentato e/o ridotta l'ampiezza.
2. Moderatamente indebolito. Determinato e rapidamente faticoso. Può presentare arresto occasionale del movimento.
3. Severamente indebolito. Frequente esitazione

nell'iniziare il movimento oppure arresto del movimento in corso.

4. Può a malapena eseguire il compito.

Rapidi movimenti alternati delle mani (movimenti di pronazione-supinazione delle mani, verticalmente o orizzontalmente, con un'ampiezza tanto larga quanto possibile, con entrambe le mani simultaneamente)

0. Normali.

1. Leggermente rallentati e/o ridotta l'ampiezza.

2. Moderatamente indeboliti. Determinato e rapidamente faticoso. Può presentare arresto occasionale del movimento.

3. Severamente indeboliti. Frequente esitazione nell'iniziare il movimento oppure arresto del movimento in corso.

4. Può a malapena eseguire il compito.

Agilità delle gambe (il paziente batte il tallone sul pavimento in rapida successione, alzando l'intera gamba. L'ampiezza dovrebbe essere di circa 8 cm)

0. Normale.

1. Leggermente rallentata e/o ridotta l'ampiezza.

2. Moderatamente indebolita. Determinata e rapidamente faticosa. Può presentare arresto occasionale del movimento.

3. Severamente indebolita. Frequente esitazione nell'iniziare il movimento oppure arresto del movimento in corso.

4. Può a malapena eseguire il compito.

Alzarsi dalla sedia (il paziente tenta di alzarsi da una sedia a schienale dritto di legno o di metallo, con le braccia incrociate sul torace)

0. Normale.

1. Lento o può necessitare di più di un tentativo.

2. Si dà la spinta mediante i braccioli della sedia

3. Tende a ricadere indietro e può dover tentare più di una volta, ma può alzarsi senza aiuto.

4. Incapace di alzarsi senza aiuto.

Postura

0. Normale eretta.

1. Non completamente eretta, postura leggermente chinata; potrebbe essere normale per le persone anziane.

2. Postura moderatamente chinata, francamente anormale; può essere moderatamente inclinata su di un lato.

3. Postura severamente chinata con cifosi; può essere moderatamente inclinata su di un lato.

4. Marcata flessione con estrema anormalità della postura.

Andatura

0. Normale.

1. Cammina lentamente, può trascinarsi a piccoli passi, ma senza festinazione o spinta.

2. Cammina con difficoltà, ma richiede poca o nessuna assistenza; può presentare qualche festinazione,

passi piccoli o spinta.

3. Severo disturbo dell'andatura; richiede assistenza.

4. Non può camminare affatto, eventualmente con assistenza.

Stabilità posturale (risponde al rapido spostamento indietro prodotto dalla trazione sulle spalle a paziente eretto con gli occhi aperti ed i piedi lievemente distanziati)

0. Normale.

1. Retropulsione, ma compensa senza aiuto.

2. Assenza di risposta posturale; potrebbe cadere se non sorretto dall'esaminatore.

3. Molto instabile, tende a perdere l'equilibrio spontaneamente.

4. Incapace di rimanere in piedi senza assistenza.

Bradicinesia ed ipocinesia corporea (combinante lentezza, esitazione, diminuita oscillazione delle braccia, ampiezza ridotta e povertà dei movimenti in generale)

0. Nessuna.

1. Lentezza minimale, conferendo movimento ad un carattere voluto, potrebbe essere normale per alcune persone. Possibilmente ridotta ampiezza.

2. Lieve grado di lentezza e povertà di movimenti che è francamente anormale. Alternativamente, una certa riduzione d'ampiezza.

3. Moderata lentezza, povertà o limitata ampiezza del movimento.

4. Marcata lentezza, povertà o limitata ampiezza del movimento.

Sezione IV

COMPLICANZE DELLA TERAPIA (NELLA SETTIMANA TRASCORSA)

A. DISCINESIE

Durata: in che percentuale si presentano le discinesie durante lo stato di veglia? (informazioni anamnestiche)

0. Nessuna.

1. 1—25% della giornata.

2. 26—50% della giornata.

3. 51—75% della giornata.

4. 76-100% della giornata.

Invalidità: quanto invalidanti sono le discinesie? (informazioni anamnestiche; possono essere modificate attraverso l'accertamento d'ufficio)

0. Non invalidanti.

1. Lievemente invalidanti.

2. Moderatamente invalidanti.

3. Severamente invalidanti.

4. Completamente invalidanti.

Discinesie dolorose: quanto dolorose sono le discinesie?

- 0. Assenza di discinesie dolorose.
- 1. Lievi.
- 2. Moderate
- 3. Severe.
- 4. Marcate.

Presenza di distonia mattutina (notizie anamnestiche)

- 0. No
- 1. Sì

B OSCILLAZIONE CLINICA

Ci sono dei periodi prevedibili di "off" come a determinare il tempo successivo ad una dose di farmaco?

- 0. No.
- 1. Sì.

Ci sono dei periodi imprevedibili di "off" come a determinare il tempo successivo ad una dose di farmaco?

- 0. No.
- 1. Sì.

I periodi di "off" insorgono rapidamente? (per esempio in pochi secondi)

- 0. No.
- 1. Sì.

In quale percentuale il paziente presenta uno stato di "off" nello stato di veglia?

- 0. Nessuna.
- 1. 1-25% della giornata.
- 2. 26-50% della giornata.
- 3. 51-75% della giornata.
- 4. 76-100% della giornata.

C ALTRE COMPLICANZE

Il paziente presenta anoressia, nausea o vomito?

- 0. No
- 1. Sì.

Il paziente presenta qualche disturbo del sonno? (per esempio, insonnia o ipersonnia)

- 0. No.
- 1. Sì.

Il paziente presenta ortostatismo sintomatico?

- 0. No.
- 1. Sì.

Registrare la pressione arteriosa, la frequenza ed il peso del paziente, sotto forma di punteggio

DIARIO DELLE 24 ORE

Data..... Iniziali..... Sede.....

Compilare il diario due volte la settimana in giorni non consecutivi

TEMPO a partire da mezzanotte	ON Stato di sblocco senza discinesie fastidiose	ON Stato di sblocco con discinesie fastidiose	OFF Stato di blocco	SONNO	TEMPO a partire da mezzogiorno	ON Stato di sblocco senza discinesie fastidiose	ON Stato di sblocco con discinesie fastidiose	OFF Stato di blocco	SONNO
00:00-00:30					12:00-12:30				
00:30-01:00					12:30-13:00				
01:00-01:30					13:00-13:30				
01:00-02:00					13:30-14:00				
02:00-02:30					14:00-14:30				
02:30-03:00					14:30-15:00				
03:00-03:30					15:00-15:30				
03:30-04:00					15:30-16:00				
04:00-04:30					16:00-16:30				
04:30-05:00					16:30-17:00				
05:00-05:30					17:00-17:30				
05:30-06:00					17:30-18:00				
06:00-06:30					18:00-18:30				
06:30-07:00					18:30-19:00				
07:00-07:30					19:00-19:30				
07:30-08:00					19:30-20:00				
08:00-08:30					20:00-20:30				
08:30-09:00					20:30-21:00				
09:00-09:30					21:00-21:30				
09:30-10:00					21:30-22:00				
10:00-10:30					22:00-22:30				
10:30-11:00					22:30-23:00				
11:00-11:30					23:00-23:30				
11:30-12:00					23:30-00:00				

Frontal Assessment Battery (FAB)

B Dubois-B Pillon-A Slachevsky-I Litvan

Hôpital del la Salpêtrière, 75013 Paris, France

Sei test da usare al letto del paziente (non richiedono più di 10 minuti)

1. Somiglianza (concettualizzazione)

- *"In che cosa sono simili :*
- *una banana e un'arancia*

(In caso di fallimento totale: "non sono simili" o di fallimento parziale: "entrambe hanno la buccia", aiutare il paziente: " *la banana e l'arancia sono entrambe*"; ma assegnare 0 a questa risposta; non aiutare il paziente per i due successivi item)

- *un tavolo e una sedia?*
- *Un tulipano, una rosa e una margherita?"*

- **punteggio** : solo le risposte categoriali (frutta, mobili, fiori) sono considerate corrette.

3 risposte corrette	3
2 risposte corrette	2
1 risposta corretta	1
nessuna risposta corretta	0

2. Fluenza fonemica (flessibilità mentale)

- *"Dica il maggior numero possibile di parole che cominciano con la lettera "S", qualsiasi parola eccetto cognomi o nomi propri".*

Se il paziente non dà nessuna risposta nei primi 5 secondi, dire: "Per esempio, serpente". Se il paziente si ferma per oltre 10 secondi, stimolarlo dicendo: "Qualsiasi parola che cominci con la lettera "S". La prova dura 60 secondi.

- **Punteggio**: ripetizioni o variazioni (scarpa, scarpone), cognomi o nomi propri non sono contate come risposte corrette.

Più di 9 parole	3
Da 6 a 9 parole	2
Da 3 a 5 parole	1
Meno di 3 parole	0

3. Serie Motorie (programmazione)

- *"Guardi con attenzione quello che faccio".*

L'esaminatore seduto di fronte al paziente effettua tre volte, da solo, con la mano sinistra la serie di Luria "pugno-taglio-piatto".

- *"Ora faccia lo stesso, con la mano destra prima con me poi da solo".*

L'esaminatore effettua tre volte la stessa serie con il paziente, poi gli dice: "continui da solo"

- **Punteggio**:

- il paziente effettua da solo, correttamente, 6 serie consecutive	3
- il paziente effettua da solo, correttamente, almeno 3 serie consecutive	2
- il paziente sbaglia da solo, ma effettua correttamente almeno 3 serie consecutive con l'esaminatore	1
- il paziente non riesce ad effettuare 3 serie consecutive neppure con l'esaminatore.	0

C:\Documents and Settings\UK\Documents\PSICO\Test-Scales\FAB.doc

4. Istruzioni contrastanti (sensibilità all'interferenza)

- "Batta due volte quando io batto una volta".

Per essere sicuri che il paziente abbia capito le istruzioni, si effettua una serie di tre prove :
1-1-1.

- "Batta una volta quando io batto due volte".

Per essere sicuri che il paziente abbia capito le istruzioni, si effettua una serie di tre prove :
2-2-2.

L'esaminatore effettua la serie seguente : 1-1-2-1-2-2-2-1-1-2.

- punteggio :
 - nessun errore 3
 - 1 o 2 errori 2
 - più di 2 errori 1
 - il paziente batte come l'esaminatore per almeno 4 prove consecutive 0

5. Go – No - Go (controllo inibitorio)

- "Batta una volta quando io batto una volta".

Per essere sicuri che il paziente abbia capito le istruzioni, si effettua una serie di tre prove : 1-1-1.

- "Non batte quando io batto due volte".

Per essere sicuri che il paziente abbia capito le istruzioni, si effettua una serie di tre prove : 2-2-2-2.

L'esaminatore effettua la serie seguente : 1-1-2-1-2-2-2-1-1-2.

- punteggio :
 - nessun errore 3
 - 1 o 2 errori 2
 - più di 2 errori 1
 - il paziente batte come l'esaminatore per almeno 4 prove consecutive 0

6. Comportamento di prensione (autonomia ambientale)

- L'esaminatore è seduto di fronte al paziente. Mettere le mani del paziente con le palme in alto, appoggiate sulle ginocchia. Senza dire nulla e senza guardare il paziente, l'esaminatore porge le sue mani vicino a quelle del paziente e ne tocca le palme, contemporaneamente da ambo i lati, osservando se il paziente spontaneamente le afferra. Se il paziente le afferra, l'esaminatore prova di nuovo dopo avergli detto: "Non prenda le mie mani"

- punteggio :
 - il paziente non afferra le mani dell'esaminatore 3
 - il paziente e viceversa chiede cosa deve fare 2
 - il paziente afferra le mani senza esitazione 1
 - il paziente afferra le mani dell'esaminatore anche dopo che gli ha chiesto di non farlo 0

TOTALE/18

DIGIT SPAN

Ora le leggerò una serie di numeri e lei li dovrà semplicemente ripetere nello stesso ordine. Non appena avrò finito le farò un cenno con la mano e lei inizierà a ripetere. Non cominci prima che io abbia finito. Inizierò con pochi numeri e poi aumenterò fino a quando lei riuscirà a ripeterli tutti.

Per esempio, se io dico: 7, 9 lei ripete:

Se ha compreso, allora si prosegue.

Allora, cominciamo:

5-8-2	3	6-1-9-4-7-3	6
6-9-4	3	3-9-2-4-8-7	6
7-2-8-6	4	5-9-1-7-4-2-8	7
8-5-3-9	4	4-1-7-9-3-8-6	7
4-2-7-3-1	5	5-8-1-9-2-6-4-7	8
7-5-8-3-6	5	3-8-2-9-5-1-7-4	8

Punti/8

Osservazioni

TRAIL MAKING TEST (TMT)

I foglio di prova: su questo foglio (*si indica*) sono distribuiti dei numeri. Lei dovrà partire dal numero 1, INIZIO, e tracciare una linea per raggiungere il 2, poi andare al 3, poi al 4 e così via fino a dove c'è scritto FINE. Dovrà cercare di non staccare la matita dal foglio. Non si preoccupi se le linee non sono dritte, non importa, cerchi solo di essere il più possibile veloce e accurato nella ricerca.

II foglio: su questo foglio (*si indica*) ci sono più numeri, ma il suo compito è il medesimo. Ora deve essere veloce e accurato, perché calcolerò quanto tempo impiega. Pronto?

TMT-A	Tempo*	Errori
Esecuzione

* Sempre in secondi

Osservazioni

Solo se è riuscito a svolgere il TMT-A si passa alla prova successiva, TMT-B:

I foglio di prova: su questo foglio (*si indica*) sono distribuiti sia numeri sia lettere dell'alfabeto (*accertarsi della conoscenza dell'alfabeto*). Lei dovrà congiungere con una linea, come prima, i numeri e le lettere in ordine crescente e in modo alternato a partire dal numero 1, INIZIO, e deve alternare sempre un numero e una lettera, un numero e una lettera. Dal numero 1 deve tracciare una linea per raggiungere la prima lettera A, poi da qui il secondo numero 2, da qui la seconda lettera B, poi il numero 3, poi la lettera C, poi 4, poi D, dove c'è scritto FINE. Dovrà fare tutto questo velocemente, sia la ricerca di numeri e lettere sia la traccia, e cercare di non staccare la matita dal foglio. Non si preoccupi se le linee non sono dritte, cerchi solo di essere il più possibile veloce e accurato nella ricerca.

II foglio: su questo foglio (*si indica*) ci sono più numeri e più lettere, ma il suo compito è il medesimo. Deve essere veloce e accurato, perché ora calcolerò quanto tempo impiegherà. Pronto?

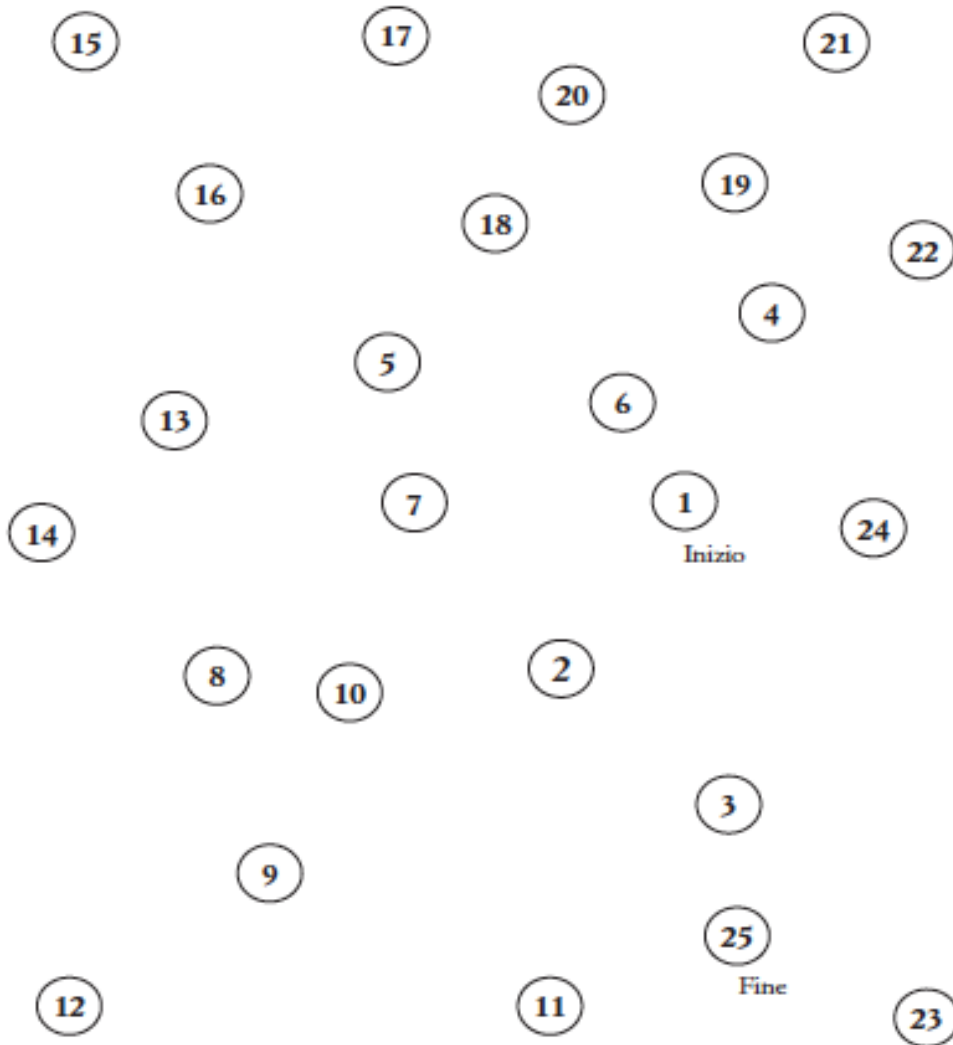
TMT-B	Tempo	Errori
Esecuzione

Osservazioni

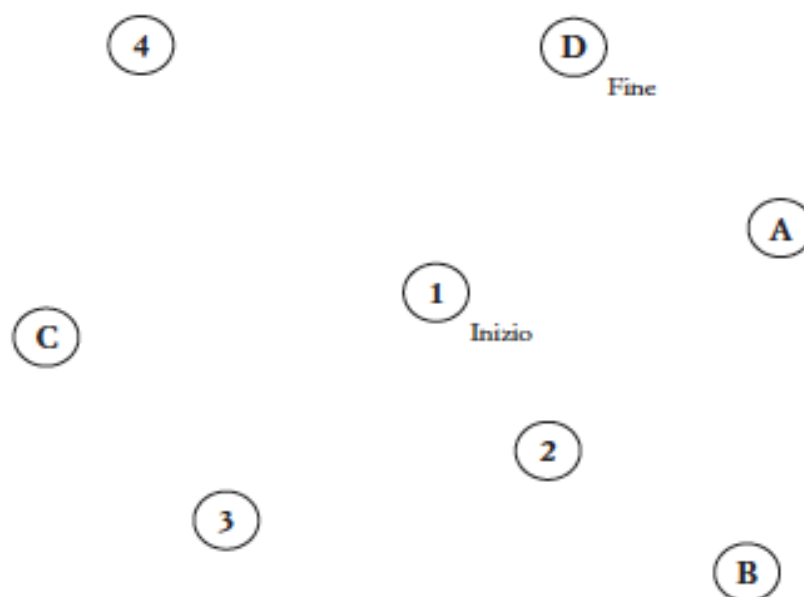
Osservazioni	<input type="checkbox"/> Non comprende come eseguire la prova	Prova
	<input type="checkbox"/> Comprende come eseguire la prova	MTA



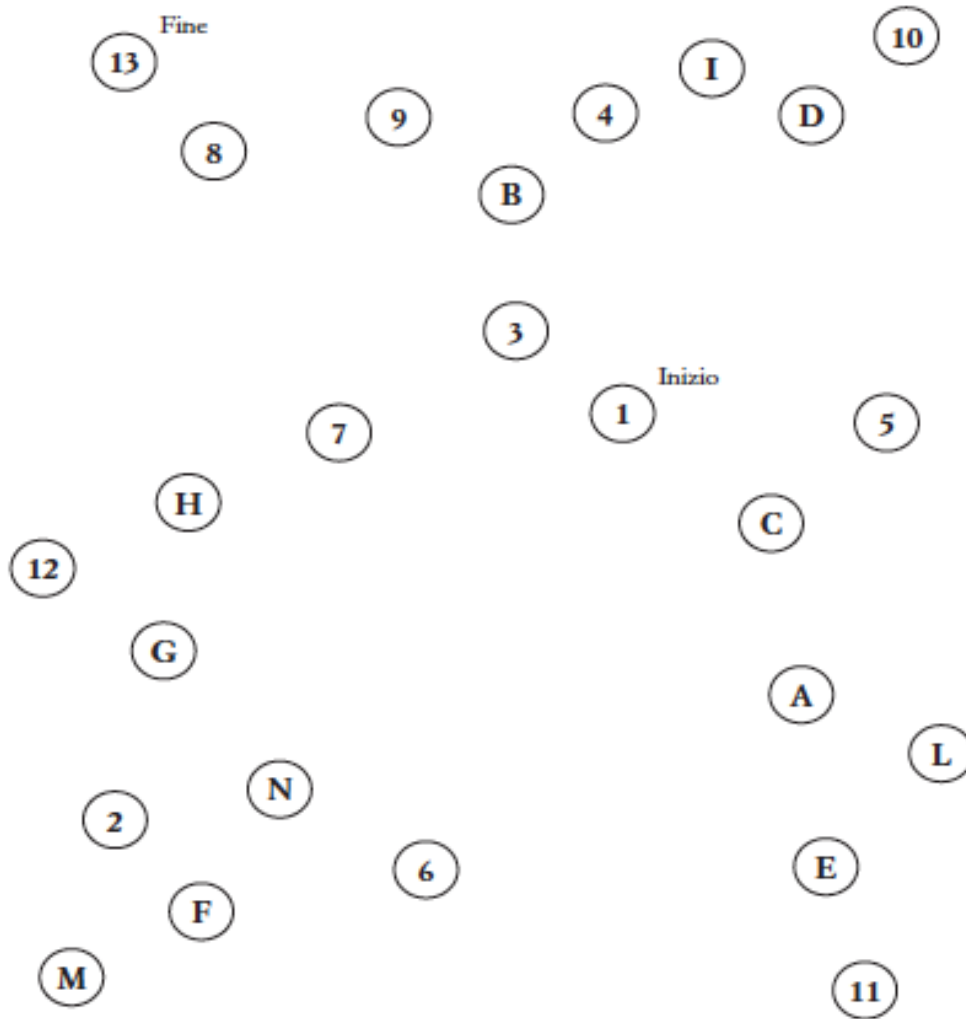
.....	Esecuzione
Errori	Tempo	IMTA



Osservazioni	<input type="checkbox"/> Non comprende come eseguire la prova	Prova
	<input type="checkbox"/> Comprende come eseguire la prova	MT 8



.....
Errori	Tempo	MT-8



MEMORIA CON INTERFERENZA

10 e 30 secondi

Ora le mostrerò tre lettere (*presentare i cartoncini*) che lei deve leggere ad alta voce e cercare di memorizzare. Poi le coprirò e più avanti gliele chiederò di nuovo, quindi cerchi di tenerle in memoria. Intanto, la farò contare di due in due a partire da un numero che sarà sempre diverso, ora è 15, quindi cominci 15, 17... (*Dopo 10 secondi*): Bene, smetta di contare e mi dica: si ricorda le tre lettere di prima? *Se comprende la prova si prosegue. Se nella parte a 10 secondi ottiene una prestazione nulla si ritiene non eseguibile la parte a 30 secondi.*

	Stimolo	N di partenza	Risposta	Lettere e posizioni corrette	Solo lettere
Prova	S D F	15			
10 sec.	F G L	8			
10 sec.	P M T	21			
10 sec.	C R B	93			

Punti a 10 sec. /9 /9

30 sec.	Z L R	6			
30 sec.	Q V S	91			
30 sec.	D N C	87			

Punti a 30 sec. /9 /9

Osservazioni

FLUENZA FONEMICA

Ora deve dirmi tutte le parole che le vengono in mente che iniziano per una certa lettera, ricordi però di non dire nomi di persona o città.

Cominciamo con la lettera C, per esempio parole come *casa, ciliegia...*, su vada avanti lei (1 minuto)

1	2	3	4	5	
6	7	8	9	10	
11	12	13	14	15	
16	17	18	19	20	
21	22	23	24	25	
26	27	28	29	30	
31	32	33	34	N. totale	

Ora parole che iniziano con la lettera P come *pasta, prezzo...*

(1 minuto)

1	2	3	4	5	
6	7	8	9	10	
11	12	13	14	15	
16	17	18	19	20	
21	22	23	24	25	
26	27	28	29	30	
31	32	33	34	N. totale	

Ora parole che iniziano con la lettera S come *sole, scivolo...*

(1 minuto)

1	2	3	4	5	
6	7	8	9	10	
11	12	13	14	15	
16	17	18	19	20	
21	22	23	24	25	
26	27	28	29	30	
31	32	33	34	N. totale	

Ripetizioni (R) Intrusioni (I).....

Punti (media)



**MINI MENTAL STATE
 EXAMINATION
 -MMSE-**

DATA:.....
 NOME:.....
 ETA':..... **SCOLARITA':**.....

<p>ORIENTAMENTO TEMPORALE <i>(Iniziare con le 5 domande che riguardano l'orientamento temporale nell'ordine elencato - 1 punto per ogni risposta corretta – max 5p.ti) Mi sa dire in che anno siamo?</i> In che stagione? In che mese? In che giorno del mese siamo? E in che giorno della settimana siamo?</p>	<p>ANNO.....[] STAGIONE.....[] MESE.....[] GIORNO DEL MESE.....[] GIORNO DELLA SETTIMANA.....[]</p>	<p>... /5</p>
<p>ORIENTAMENTO SPAZIALE <i>(Iniziare con le 5 domande che riguardano l'orientamento spaziale nell'ordine elencato - 1 punto per ogni risposta corretta – max 5p.ti) –</i> Mi sa dire in che regione siamo? In che provincia? In che città siamo? Sa dirmi come si chiama questo posto, questo edificio? A che piano siamo?</p>	<p>REGIONE.....[] PROVINCIA.....[] CITTA'.....[] POSTO.....[] PIANO.....[]</p>	<p>... /5</p>
<p>REGISTRAZIONE <i>(Leggere le 3 parole e chiedere immediatamente le parole lette - 1 p.to a parola ripetuta correttamente e nell'ordine corretto – max 3p.ti) – Adesso ascolti e ripeta le parole che le leggerò, esattamente nello stesso ordine</i></p>	<p>CASA – PANE – GATTO [] - [] - []</p>	<p>... /3</p>
<p>CALCOLO <i>(Iniziare con la prova di sottrazione a partire dalla cifra 100 e togliere poi il numero 7. Possibile dare UN SOLO suggerimento 1 p.to per risposta corretta o 1.p.to per sottrazione corretta rispetto all'ultima cifra detta – max 5p.ti) –</i> Adesso faremo qualche calcolo. Deve partire dal numero 100 e sottrarre 7. Dal risultato toglie ancora 7 e così via fino a quando non la fermo. Incominciamo, 100-7?</p> <p>SPELLING ALL'INDIETRO <i>(Eseguire solo nel caso in cui il paziente non riporti il punteggio pieno di 5/5 alla prova di calcolo. Contare quante parole sono sillabate correttamente e nella corretta successione inversa della parola CARNE 1p.to per ogni lettera corretta nella corretta posizione – max 5p.ti) –</i> La parola CARNE è formata da 5 lettere. Le chiedo di dirmi queste lettere, dall'ultima, ad una ad una fino alla prima</p>	<p>93 - 86 - 79 - 72 - 65 [] - [] - [] - [] - []</p> <p>..... [] - [] - [] - [] - []</p> <p>E - N - R - A - C [] - [] - [] - [] - []</p>	<p>... /5</p>
<p>RIEVOCAZIONE <i>(Far rievocare 3 parole 1p.to a parola ripetuta correttamente l'ordine non conta – max 3p.ti) –</i> Ricorda le 3 parole che le ho letto poco fa e che lei ha ripetuto?</p>	<p>CASA – PANE – GATTO [] - [] - []</p>	<p>... /3</p>
<p>DENOMINAZIONE <i>(Mostrare una matita e un orologio, non allacciato al polso. Chiedere al paziente di dire il nome dei due oggetti presentati uno dopo l'altro 1p.to per ogni oggetto correttamente riconosciuto – max 2p.ti) –</i> Sa dirmi il nome di questo oggetto? E il nome di questo?</p>	<p>MATITA [] OROLOGIO []</p>	<p>... /2</p>
<p>RIPETIZIONE DI FRASE <i>(Chiedere al paziente di ripetere la frase letta max 1p.to) –</i> Adesso le leggerò una frase, uno sciogli-lingua. Mi ascolti attentamente e lo ripeta senza errori.</p>	<p>TIGRE CONTRO TIGRE</p>	<p>... /1</p>
<p>ORDINE ORALE <i>(Si richiede al paziente di eseguire una serie di istruzioni comunicate. Non è possibile dare suggerimenti o ripetere l'ordine - 1p.to per ogni istruzione compiuta correttamente – max 3p.ti) –</i> Prenda questo foglio con la mano destra/sinistra (mano dominante), lo pieghi a metà e poi me lo restituisca.</p>	<p>MANO DESTRA/sinistra - PIEGARE - RESTITUIRE [] - [] - []</p>	<p>... /3</p>
<p>ORDINE SCRITTO <i>(Se permangono errori di lettura passare alla prova successiva e attribuire p.teggio pari a 0. Se è necessario chiedere espressamente di chiudere gli occhi attribuire p.teggio pari a 0 max 1p.to per esecuzione come da istruzioni) –</i> Presentare al paziente il foglio con scritto “CHIUDI GLI OCCHI” e chiedere di leggerlo. Fare in modo che il paziente legga il correttamente. Successivamente chiedere al paziente: “E’ un ordine, deve fare quello che è scritto”.</p>		<p>... /1</p>
<p>SCRITTURA <i>(Chiedere al paziente di scrivere una frase. La frase dovrebbe avere almeno un soggetto ed un verbo max 1p.to) –</i> Vede questo foglio? Le chiedo di scrivere qui una frase, un pensiero che ha in mente.</p>		<p>... /1</p>

PRASSIA COSTRUTTIVA

*(Mostrare al paziente i due pentagoni incrociati e chiedere di ricopiarli uguali nello spazio adiacente max 1p.to) –
Vede questa figura. Le chiedo di copiarla uguale.*

...
/1

PUNTEGGIO GREZZO: .../30

PUNTEGGIO CORR. : .../30

