

UNIVERSITA'
DEGLI STUDI DI
PADOVA

Università degli Studi di Padova
Dipartimento di Psicologia Generale

SCUOLA DI DOTTORATO DI RICERCA IN SCIENZE PSICOLOGICHE
INDIRIZZO PSICOBIOLOGIA
CICLO XXIV

COGNITIVE AND ELECTROENCEPHALOGRAPHIC MARKERS OF HEALTHY AND PATHOLOGICAL AGING

Direttore della Scuola: Ch.ma Prof.ssa Clara Casco

Coordinatore d'indirizzo: Ch.mo Prof. Alessandro Angrilli

Supervisore: Ch.ma Prof.ssa Patrizia Silvia Bisiacchi

Dottoranda: Giorgia Cona

Alle mie nonne

Index

SUMMARY 5
RIASSUNTO 17

GENERAL INTRODUCTION 29

PART I:

Cognitive and Electroencephalographic Markers of Healthy Aging 33

CHAPTER 1 THEORIES OF AGING 35
1.1 BASIC COGNITIVE CHANGES IN AGING: AN OVERVIEW 35
1.2 MAIN THEORIES OF COGNITIVE AGING 39
1.2.1 Sensory deficit theory 39
1.2.2 The processing-speed theory 40
1.2.3 Resources deficit theory 41
1.2.4 Inhibition deficit theory 42
1.2.5 Theory of Cognitive Control 43
1.2.6 CRUNCH model 45
1.2.7 Scaffolding Theory of Aging and Cognition 47

CHAPTER 2 AGING AND PROSPECTIVE MEMORY 49
2.1 PROSPECTIVE MEMORY: FEATURES AND MODELS 49
2.1.1 Introduction 49
2.1.2 Phases of Prospective Memory 51
2.1.3 Models of Prospective Memory 53
2.1.4 Time-based versus event-based prospective memory tasks 57

2.2 AGE-RELATED CHANGES IN PROSPECTIVE MEMORY 61
2.2.1 An overview of Aging and PM 61
2.2.2 Age effects on time-based and event-based PM tasks 63
2.2.3 Age effects on time-based tasks: the role of Time Monitoring 65
2.2.4 Factors influencing the magnitude of age-related differences in PM tasks 67

2.3 AGE-RELATED CHANGES IN PM: ELECTROPHYSIOLOGICAL EVIDENCE 71
2.3.1 Age effects on ERPs associated with PM cues 71
2.3.2 Age effects on ERPs associated with strategic monitoring 73

2.4 EXPERIMENT 1: ERP MECHANISMS UNDERLYING AGE-RELATED ALTERATIONS IN TIME-BASED PROSPECTIVE MEMORY 75
2.4.1 Introduction 75
2.4.2 Methods 81
2.4.3 Results 85
2.4.4 Discussion 95

CHAPTER 3 AGING AND EXECUTIVE CONTROL 101
3.1 AGING AND EXECUTIVE CONTROL: AN OVERVIEW 101
3.2 AGE-RELATED CHANGES IN INHIBITION 103
3.2.1 Inhibitory processes 103
3.2.2 Inhibitory processes in aging 108
3.2.3 ERP correlates of age-related differences in inhibitory processes 112

3.3 AGE-RELATED CHANGES IN SHIFTING AND UPDATING 115
3.3.1 Shifting processes 115
3.3.2 Updating *versus* attentional switching 118
3.3.3 Shifting and updating processes in aging 119
3.3.4 ERP correlates of age-related differences in shifting and updating processes 121

3.4 EXPERIMENT 2: INFLUENCE OF AGING ON ERP CORRELATES OF EXECUTIVE CONTROL PROCESSES 127
3.4.1 Introduction 127
3.4.2 Methods 132
3.4.3 Results 136
3.4.4 Discussion 145

PART II:

Cognitive and Electroencephalographic Markers of Minimal Hepatic Encephalopathy 151

CHAPTER 4 MINIMAL HEPATIC ENCEPHALOPATY 153

4.1 HEPATIC ENCEPHALOPATHY 153

4.1.1 Pathogenesis and aetiology of HE 154

4.1.2 Neuropsychological characterization of HE 157

4.1.3 Neurophysiological characterization and assessment of HE 160

4.2 MINIMAL HEPATIC ENCEPHALOPATHY 165

4.2.1 Neuropsychological profile of MHE 165

4.2.2 Neurophysiological profile of MHE 168

4.2.3 Traditional assessment for the diagnosis of MHE 170

4.3 EXPERIMENT 3: TESTING AND IMPROVING THE INHIBITORY CONTROL TASK TO DETECT MINIMAL HEPATIC ENCEPHALOPATHY. 173

4.3.1 Introduction 173

4.3.2 Methods 174

4.3.3 Results 178

4.3.4 Discussion 183

4.4 EXPERIMENT 4: ELECTROPHYSIOLOGICAL ALTERATIONS IN MINIMAL HEPATIC ENCEPHALOPATHY EXAMINED USING THE ICT. 187

4.4.1 Introduction 187

4.4.2 Methods 190

4.4.3 Results 193

4.4.4 Discussion 201

4.5 EXPERIMENT 5: THE IIV OF P300 AS AN INDEX FOR DETECTING NEURAL DYSFUNCTIONS IN PATIENTS WITH LIVER CIRRHOSIS 205

4.5.1 Introduction 205

4.5.2. Methods 208

4.5.3 Results 213

4.5.4 Discussion 222

GENERAL CONCLUSIONS 225

References 227

SUMMARY

The present thesis is composed of two main parts. In the first part, the effect of aging was investigated on performance and on event-related potentials (ERPs) associated with several goal-directed cognitive tasks. In the second part, cognitive and ERP changes were explored in patients with minimal hepatic encephalopathy, a syndrome characterized by cognitive and neurophysiological abnormalities in patients with liver cirrhosis.

1° PART: COGNITIVE AND ELECTROPHYSIOLOGICAL ALTERATIONS ASSOCIATED WITH HEALTHY AGING.

It is a truism that as people grow older, performance on a large number of cognitive tasks declines. These age-sensitive tasks include simple and choice reaction times (RTs) tasks, tests of episodic memory, working-memory tasks, tasks involving executive functions, spatial and reasoning abilities, mental rotation (e.g., Kausler, 1991; Salthouse, 1991). Given that deficits are so widespread across the cognitive domains, it is reasonable to assume that a limited number of mechanisms might be responsible. Different theories tried to address this issue. Some of them suggested that cognitive deficits in aging are due to a reduction in the amount of attentional resources (Craik, 1986; Craik & Byrd, 1982), or a slowing down of processing speed (Salthouse, 1996), or a decline in the inhibitory control of working-memory contents (Hasher & Zacks, 1988).

One explanation that has recently gained some prominence is the increasing impairment of executive control with age, likely related to age-specific changes in prefrontal cortex ("theory of Cognitive Control", also called "goal maintenance account"; Braver & West, 2008; Raz, 2000; West, 1996). Executive control is intended as the ability to represent, maintain and update goal information in order to exert control over behaviour and thoughts (Cohen et al., 1996). According to Miyake and collaborators (2000), executive control is not a single function, but is composed of several cognitive sub-processes, namely shifting, updating and inhibition.

To explore the role of executive control in explaining the age-related cognitive decline,

the effect of cognitive aging was measured on those tasks involving high recruitment of such ability. Specifically, the first study of the present thesis (Experiment 1) investigated the age-related changes on a time-based prospective memory (PM) task, and focused on exploring the effect of aging on ERPs. Time-based PM refers to the ability of remembering to perform an action at a specific point in the future, (for example, remembering to attend an appointment at 3 pm; Brandimonte et al., 1996; Einstein & McDaniel, 2000; Kliegel et al., 2009). A fundamental process required for successfully accomplishing PM tasks is the ability to maintain and update the PM intentions (i.e., goal information) active in memory. Such ability, being impaired based on the "theory of cognitive control", might be the factor determining the age-related alterations observed in time-based PM tasks. The analysis of ERPs elicited in time-based PM tasks is useful to test this hypothesis, and to better clarify the mechanisms responsible for age-related alterations in these kinds of tasks.

The second study focused on the relationship between executive control and cognitive aging by comparing performance of older and younger adults on a task in which the executive control load was manipulated. The task, called Inhibitory Control task (ICT; Bajaj et al., 2008a), is indeed composed of three different conditions, which varies for the executive resources needed. I expected that, if the executive control is the key factor responsible for cognitive impairment in aging, thus the deleterious effect of age on performance would be greater as the executive load increases. Moreover, ICT provides an investigation of the age-related alterations on ERPs associated with the different processes composing executive control, such as updating, shifting, and response inhibition (Miyake et al., 2000).

The two studies will be described in details below.

Experiment 1: ERP mechanisms underlying age-related alterations in Time-Based Prospective Memory

There is a general agreement, across studies on PM, towards a deleterious effect of age on time-based PM performance (Bastin & Meulemans, 2002; McDaniel & Einstein, 1992; Park et al., 1997; see Henry, MacLeod, Phillips, & Crawford, 2004, for a review).

According to Craik's theory (Craik, 1986), since in PM tasks there are no explicit prompts from the environment that instigate the retrieval of intention, individuals need to engage self-initiated and attentional demanding processes to retrieve the PM intentions.

Given that aging is associated with a reduction in the availability of these attentional resources, thus PM performance would be altered in older people.

On the other hand, according to the "theory of cognitive control" (or "goal maintenance account"; Braver & West, 2008), older adults have difficulties in the maintenance of goal representations over an extended period. In the case of time-based PM, failure to maintain active the goal (i.e., the intention) would lead to failure to correctly execute the intended action.

Although a large number of studies investigated the impairment of time-based PM with aging, nevertheless none study has ever focused on neural activity underpinning such alterations. Therefore, in order to shed light on such poorly investigated issue, the present study explored the age-related alterations in the electrophysiological correlates of time-based PM tasks.

To this end, ERPs associated with ongoing task (i.e., a task executed concurrently with the PM task) were examined in 18 older and 15 younger adults and compared between a baseline block, in which individuals were required to perform merely the ongoing task; and a PM block, in which individuals were required to perform simultaneously the ongoing and the PM tasks. The ongoing task consisted in evaluating in five-letter strings whether the letters in second and fourth positions (target positions) were equal or different by pressing one of two possible keys. In the PM task, participants were required to remember to press the "PM key" every five minutes from the beginning of the block. To help them to estimating the passing of time, they had the opportunity to check the digital clock in any moment of the task by pressing another key. The ERPs were locked to ongoing trials (i.e., the strings of letter). Reaction times, accuracy and ERPs relative to ongoing trials were compared between the baseline and the PM block, for both younger and older adults. Moreover, the percentage of accuracy in PM task and the number of clock checks were recorded.

Concerning the behavioural results, older adults showed a lower percentage of accuracy in PM task respect to younger adults. Moreover, the older adults displayed a slowing down of RTs in the ongoing task, both in the baseline and in PM block, as compared to younger adults.

Concerning the ERPs of younger adults, the addition of a time-based PM task to an ongoing activity led to a sustained positive modulation of the ERPs elicited by the ongoing trials, mainly expressed over prefrontal and frontal regions. This frontal activity seems to

reflect the load of maintaining the intention active in memory, as recently suggested (Cona et al., in press; West et al., 2011). On the other hand, in older adults these ERP modulations were more expressed over posterior regions. Interesting, a difference in the ERP amplitude between baseline and PM block was observed over prefrontal sites in younger adults (with the ERPs being more positive in PM block), but not in older adults. At first glance, the absence of the prefrontal mofulation in older adults seems to reflect their difficulties in keeping the PM intention in mind, as suggested by the "theory of cognitive control" (Braver & West, 2008).

Nevertheless, the exploration of the ERP differences as observed between the two groups in the baseline block allowed to better clarify the mechanisms responsible of these age-related changes in PM. Indeed in baseline block, compared to younger adults, older adults showed a lower P300 over parietal regions, and a higher P300 over prefrontal regions. The anteriorisation of the P300 shown by older adults has been well documented in literature (Daffner et al., 2006; 2011), and it is supposed to reflect the greater recruitment of attentional resources to compensate for olders' difficulties in the ongoing task.

Taken together, these results suggest that older adults had difficulties already in the baseline block, and cope with such difficulties by recruiting additional frontal resources (as reflected by the anteriorisation of P300). If too many resources were allocated to perform the ongoing task, then fewer resources would be available to adequately maintain the intentions in memory, leading to an impaired PM performance. Therefore, it seems more reasonable that the decline in executive control, required for intention maintenance, is not the primary cause of the age-related changes in PM tasks, but rather is itself the consequence of a reduced amount of available resources, as postulated by Craik's theory (1986).

Experiment 2: Influence of aging on ERP correlates of executive control processes

According to the "theory of cognitive control" (Braver & West, 2008), an age-related impairment in executive control is hypothesized to determine specific decrements in those cognitive tasks that are more demanding for that function. In order to test this prediction, we adopted the Inhibitory Control task (ICT; Bajaj et al., 2008a). During the ICT, a

continuous stream of letters is presented, very quickly, one after the other. In the first part of the task, it is required to respond by pressing a key only to the target letters (i.e., "X" and "Y,"). Trials containing a target letter are labelled as *Detect trials*. In the second part, it is required to respond whenever the target letters are alternated (*Go trials*), as when an "X" is preceded by a "Y", or *vice versa*, regardless of the irrelevant letters presented between them. In contrast, it must withhold response if target letters are repeated (*Nogo trials*), as when an "X" precedes another "X", or a "Y" precedes another "Y". In light of this, ICT includes trials requiring different demands of executive control. *Detect trials* requires to merely pay selective attention and to respond to specific stimuli. These trials are relatively low demanding in terms of executive control. *Go trials* are more demanding, implying the process of working memory updating. Finally, *Nogo trials* are the highest demanding trials since imply not only an updating process but also inhibitory control of response. According to the theory of control, differences on ICT performance between younger and older adults should be lowest in detect trials, intermediate in go trials and greatest in nogo trials.

Furthermore, this study was aimed at investigating the effect of age on the different processes composing the executive control (Miyake et al., 2000). Therefore it was explored the influence of aging on peak latency and amplitude of P3b, nogo-P3 and RON (i.e., reorienting negativity) components, which reflect updating, inhibition, and shifting processes, respectively. In order to better dissociate the ERP components related to these different processes, a partial least square (PLS) analysis was run. Seventeen younger and sixteen older adults performed the ICT.

Against the formulated predictions, older adults exhibited a worse performance in all kinds of trial, as from detect trials to nogo trials. More importantly, the age effect did not interact with the type of trials, hence was independent from the degree of executive control required to perform them. This means that executive control, when formulated as a unitary construct responsible for the age-related deficits in cognition, does not seem to be the elective factor for explaining the deficits shown in ICT task. In line with behavioural results, older adults showed a delay in all the ERP components studied (P3b, N2, RON, nogo-P3), regardless of the type of trial. These age-related alterations in the latency of the ERPs seem to reflect a slowing of speed of cognitive processing in the elderly individuals. Such an idea gives support to Sathouse's theory (Salthouse, 1996), which assumed that age-related cognitive decline might be due to a general reduction in the speed of processing.

Another relevant finding consists in the fact that the RON components were found particularly sensitive to aging. Specifically, these components, reflecting attentional shifting (Berti et al., 2008), were shown delayed and reduced in older adults. To my knowledge, only one study has investigated the age-related alterations in the RON components before, but utilizing an auditory distraction-paradigm (Horváth et al., 2009). Thus, the present study extended the results obtained in the work by Horváth, suggesting that the age-related impairment of attentional shifting occurred not only after distracter stimuli (as found by Horváth), but also after task-relevant ones. It suggests that in older adults shifting mechanism of attention take longer and is more effortful, probably because they are still engaged in processing the previous stimulus. Summarizing, electrophysiological and behavioural data converged in revealing that age-related cognitive impairment might be, at least partially, attributable to a general slowing of information processes. Indeed, coherently with the review by Verhaegen (2011), reduction on processing speed seems to explain cognitive deficits in elderly better than deterioration in executive control, when this is conceptualized as a unitary construct. On the other hand, a subprocess of executive control, attentional shifting, resulted particularly affected by age, and it could be another candidate to explain multiple age-related cognitive alterations.

1° Part: Conclusions

Although the present studies utilized different paradigms and tasks, they converged in revealing that executive control does not play a crucial role in determining the age-related deficits seen in these tasks. Rather, a decline in more basic, or lower-level, mechanisms seems to be the key factor to explain the multitude of age-related cognitive deficits. Specifically, the analysis of the ERPs allowed to highlight that age-related alterations were more likely due to a reduction: 1) in the amount of available resources and 2) in processing speed.

The age-related alterations concerned mainly ERPs over prefrontal regions and were they were mainly expressed as delay in the ERP latencies. Interestingly, compensatory mechanisms in older adults were also observed, and were reflected in the increase of amplitude of several components (respect to the younger adults). This led to the suggestion that aging does not simply mean cognitive and neural decline, but may also involve adaptive cognitive and neural responses.

2° PART: COGNITIVE AND ELECTROPHYSIOLOGICAL ALTERATIONS ASSOCIATED WITH MINIMAL HEPATIC ENCEPHALOPATHY.

Hepatic encephalopathy (HE) is a neuropsychiatric syndrome occurring in acute or chronic liver failure. The detection of the first, sometimes apparently negligible, signs of hepatic encephalopathy is greatly important since this condition, called minimal hepatic encephalopathy (MHE; Ferenci et al., 1998), impinges on the health-related quality of life (Groeneweg et al., 1998; Zhou et al. 2009) and it is likely to affect driving ability (Wein et al., 2004). Furthermore, it has a negative prognostic value in relation to the occurrence of both bouts of overt hepatic encephalopathy and death (Amodio et al., 1999; Romero-Gomez et al., 2007). The profile of MHE is characterized by cognitive alterations that involve selective attention and executive functions, visuomotor ability, psychomotor speed, response inhibition, and response selection (Amodio et al., 2005). MHE also causes brain dysfunction detectable by slowing of the electroencephalogram (EEG) and prolonged ERPs, such as P300 (Amodio et al., 2005; Weissenborn et al., 2005). Therefore, where possible, the diagnosis of MHE is preferably based on a combination of psychometric and neurophysiological/psychophysiological tools.

The inhibitory control task (ICT) has been recently proposed as a simple diagnostic tool for MHE (Bajaj et al., 2007; 2008a). However, its applicability to different populations of patients with cirrhosis and its relation to other measures of MHE need to be confirmed. Therefore, Experiment 3 was designed to address this issue and was aimed at assessing the specificity and sensitivity of ICT for the diagnosis of MHE. The Experiment 4 focused on the effect of MHE on the ERPs elicited by ICT, in order to highlight cognitive and electrophysiological alterations characterizing MHE.

In order to further investigate the electrophysiological alterations of MHE, another study (Experiment 5) explored the intra-individual variability (IIV) of P300 parameters (i.e., latency and amplitude) in cirrhotic patients with MHE. There is an increasing interest in IIV of cognitive performance (e.g., of RTs) within the field of cognitive neuroscience (MacDonald et al., 2006), since IIV has been widely considered to be a behavioral indicator of compromised neural mechanisms (e.g., Hultsch, et al., 2000). Nevertheless, studies establishing links between intra-individual variability in behavioral and brain responses are sparse, with most evidence being indirect. MHE seems to be a suitable model of pathology for studying this relation, given that patients with MHE showed increased IIV

of RTs (Elssas et al., 1985; Schiff et al., 2006).

Therefore, in Experiment 5, single-trial P300 parameters, obtained by means of a single-trial Bayesian estimation technique (D'Avanzo et al., 2011), were estimated to investigate the electrophysiological correlates of IIV of response speed and the relation between P300 parameters and RTs in normal individuals and in a population of patients with and without MHE.

Experiment 3 and 4:
The ICT as a suitable tool for detecting cognitive and ERP alterations in patients with liver cirrhosis

In **Experiment 3**, seventy-five patients with cirrhosis and 55 healthy controls underwent the ICT in 2 reference centers for the study of hepatic encephalopathy. Patients were evaluated for MHE by psychometric hepatic encephalopathy score (PHES) and spectral electroencephalogram analyses. Performance on go and nogo trials was compared between the two groups. Patients with cirrhosis exhibited a higher number of errors in nogo trials (i.e., ***lures***), and lower accuracy in go trials, as compared with controls. However, the number of lures was comparable among patients with and without MHE. Importantly, an inverse relation between accuracy in go trials and number of lures was shown when the go accuracy was particularly low. However this is not surprising: a low accuracy in go trials indicates that many trials had a missing response (in go trial an error is a missed response), but if a participant commits many missing responses, he/she is more likely to "perform" correctly on nogo trials (hence to not respond when actually it is required to not respond). In light of this, the low number of error in nogo trials is a spurious effect. Hence, a new variable (weighted lures) was codified, adjusting the number of lures based on go accuracy. This variable distinguished between patients with and without MHE. However, accuracy in go trials alone was as effective as a stand-alone variable. Therefore, testing inhibition (lures) does not seem to be superior to testing attention and working memory updating (go accuracy) for the detection of MHE.

In Experiment 4 the electrophysiological alterations related to cirrhosis were investigated in the ICT task by comparing ERPs in cirrhotic patients with MHE (N=13), without MHE (N=18) with ERPs in healthy controls (N=17). Specifically, the ERPs in detect, go and nogo trials were measured, reflecting processes of selective attention,

working memory updating, and inhibition, respectively. Data were further analysed by means of a PLS analysis, was particularly suited to dissociate the ERP correlates of the different subprocesses. Findings from ANOVA and PLS analysis converged in showing selective alterations of the ERPs on detect trials in patients with MHE. Specifically these included a reduction in P3a amplitude over frontocentral sites and a delay in the P3b latency. Since detect trials involve principally attentional processes, alterations on these trials may indicate that MHE is associated with an impairment of low-level cognitive abilities, such as attention. This result corroborated the claim of Experiment 3, concerning the appropriateness to test for low-level abilities (i.e., attention) before, or together with, testing for high-level abilities (i.e., inhibition) for the diagnosis of MHE (Amodio et al., 2010). The second main, and unexpected, finding was the enhancement of several ERP components (namely, the N2 and nogo-P3) in cirrhotic patients without MHE. These electrophysiological changes might be a compensatory mechanism, reflecting the allocation of additional executive resources for overcoming the difficulties of the task (indeed, also patients without MHE had a reduction of P3a, which is an index of attentional processes).

Experiment 5: The IIV of P300 as an index for detecting neural dysfunctions in patients with liver cirrhosis

In patients with cirrhosis, an increased intra-individual variability of RTs has been described and qualified as a potential early sign of brain dysfunction (Schiff et al., 2006). Unfortunately, a neural counterpart of this phenomenon was not obtained yet. However, since a reduction in the amplitude of P300 has been observed in this patient population, it is possible to hypothesize that P300 amplitude reduction depends, at least in part, on the increased variability of single-trial P300 latency (as evidenced in other pathologies; e.g., Hultsch et al., 2000). Moreover, single-trial analysis might clarify the relation between RTs and P300 parameters, and evidence how this relation changed under pathological conditions, such as MHE.

EEG was recorded during the execution of a choice reaction time task (i.e., Simon task) in 14 cirrhotic patients with MHE (diagnosed on paper & pencil tests plus EEG), 15 cirrhotic patients without MHE and 14 healthy controls matched for age and educational level. Single-trial P300 amplitude and latency, together with their standard deviation, were

obtained using a non-parametric bayesian estimation method. P300 was also measured with the classical method of averaging. RTs distribution and its relation with single-trial P300 amplitude and latency were analysed.

In cirrhotic patients, RTs were slower and more variable compared to those of controls. An increased variability in P300 latency was also detected. Linear multiple regression analysis revealed that average-based P300 amplitude reduction was predicted both by standard deviation of single-trial P300 latency and by single-trial P300 mean amplitude.

These results indicate that average-based P300 amplitude reduction in cirrhotic patients with MHE depends on both an increased variability of single-trial P300 latency, and a reduction in single-trial P300 amplitude. Interestingly, we also found that P300 latency increased and amplitude decreased in parallel with increasing RTs in normal participants, but not in cirrhotic patients with MHE. Thus, another sign of neural alteration might be the weaker relationship between RTs and P300 parameters observed in patients with MHE.

In summary, the present study suggests that, under normal conditions, a relation between P300 and RTs is detectable and the P300 is stable across trials; in contrast, when the brain does not function properly, as observed in patients with MHE, the relation between P300 and RTs vanishes, and neural responses become more variable.

2° Part: Conclusions

The use of ICT task provided several insights concerning the neural markers of MHE. Specifically, patients with MHE showed a prolongation and a reduction of the P300 components elicited in the detect trials of ICT task, reflecting deficits in selective and sustained attention. On the other side, patients without MHE displayed an enhancement of several ERP components (i.e., N2 and P3-nogo), which might reflect a compensatory neural mechanism.

The Experiment 5 better clarified the profile of P300 in cirrhotic patients. Indeed, such patients, especially those with MHE, showed an increased intra-individual variability of the P300 latency, which may contribute to the reduction of its amplitude.

GENERAL CONCLUSIONS

The ERP technique was revealed to be a powerful tool to explore neural alterations underlying both the healthy and pathological aging. Interestingly, several patterns of ERP alterations were shared by older individuals and cirrhotic patients (e.g., the delay in several ERPs, or a 'paradoxical' enhancement of other components, such as N2). Such ERP alterations highlighted that 1) age- and MHE-related deficits in higher-level cognitive tasks might be due to alterations in lower-level functions or mechanisms, including attention deficits, the reduction of available resources or processing speed; 2) brain activity of older people and cirrhotic patients without MHE was similarly characterized by compensatory mechanisms, recruited to cope with the difficulties of the tasks.

RIASSUNTO

La presente tesi si compone di due parti principali. Nella prima parte è stato studiato l'effetto dell'età sulla performance e sui potenziali evento-relati (ERP) elicitati in differenti compiti cognitivi. Nella seconda parte sono stati esplorati i cambiamenti elettrofisiologici (i.e., alterazioni a livello di ERP) e cognitivi che caratterizzano l'encefalopatia epatica minima (MHE), una sindrome neuropsichiatrica conseguente a cirrosi epatica.

1° PARTE: ALTERAZIONI COGNITIVE ED ELETTROFISIOLOGICHE ASSOCIATE ALL'INVECCHIAMENTO SANO

All'avanzare dell'età, le persone mostrano difficoltà in diversi compiti cognitivi. Tali compiti comprendono ad esempio compiti di tempi di reazione (TR) semplice o di scelta, test di memoria episodica, compiti di working memory o che coinvolgono funzioni esecutive, abilità spaziali e di ragionamento, test di rotazione mentale (e.g., Kausler, 1991; Salthouse, 1991).

Dato che tali deficit sono così diffusi tra i diversi domini cognitivi, è ragionevole assumere che essi dipendano da un'alterazione a carico di un ristretto numero di meccanismi. Diverse teorie si sono occupate di rispondere a tale questione. Alcune di queste hanno suggerito, ad esempio, che l'invecchiamento cognitivo sia associato ad una riduzione nella quantità di risorse attenzionali disponibili (Craik, 1986; Craik & Byrd, 1982), ad un rallentamento nella velocità di elaborazione (Salthouse, 1996), o ad un declino nel controllo inibitorio delle informazioni contenute nella working memory (Hasher & Zacks, 1988).

Una spiegazione cha ha recentemente ricevuto largo consenso sostiene che alla base delle alterazioni cognitive legate all'età vi sia una disfunzione a livello di controllo esecutivo, probabilmente dovuta a cambiamenti a carico della corteccia prefrontale ("teoria del controllo cognitivo" conosciuta anche come "ipotesi del mantenimento degli obiettivi"; Braver & West, 2008; Raz, 2000; West, 1996). Per controllo esecutivo si intende la capacità di rappresentare, mantenere e aggiornare gli obiettivi in memoria al fine di esercitare un controllo sui pensieri e sul comportamento (Cohen et al., 1996). Sulla base del lavoro di Miyake e collaboratori (2000), il controllo non sembra essere una funzione

unitaria, ma è composta da diversi sotto-processi cognitivi, quali lo shifting, l'aggiornamento nella working memory e l'inibizione.

Per esaminare il ruolo che ha il controllo esecutivo nello spiegare il declino cognitivo legato dell'invecchiamento, è stato testato l'effetto dell'età in quei compiti che sono stati dimostrati richiere un alto coinvolgimento di controllo esecutivo. In particolare, il primo studio di questa tesi (Esperimento 1) ha esaminato i cambiamenti, legati all'età, in un compito di memoria prospettica (MP) basata sul tempo, focalizzandosi sull'analisi di quelle modulazioni ERP che rifletterebbero il declino della MP nell'invecchiamento. La memoria prospettica basata sul tempo si riferisce infatti all'abilità di ricordarsi di eseguire un'azione in un particolare momento nel futuro (ad esempio, ricordarsi di andare ad un appuntamento alle tre; Brandimonte et al., 1996; Einstein & McDaniel, 2000; Kliegel et al., 2009). Un processo che è fondamentale per eseguire appropriatamente i compiti prospettici è il mantenimento e l'aggiornamento delle intenzioni prospettiche in memoria (che rappresentano altresì gli obiettivi del compito prospettico). Tali processi di mantenimento, essendo alterati nell'invecchiamento secondo la teoria del controllo cognitivo, potrebbero essere quindi il fattore chiave nel determinare le alterazioni osservate nei compiti di MP. L'analisi degli ERP elicitati dal compito prospettico si è rivelata utile per testare tale ipotesi, e per chiarire quali siano i meccanismi responsabili del declino in questo tipo di compiti.

Il secondo studio ha indagato la relazione tra controllo esecutivo e invecchiamento cognitivo confrontando la prestazione di individui giovani e quella di individui più anziani in un compito in cui veniva variato il carico di controllo esecutivo tra le condizioni. Il compito, chiamato Inhibitory Control Task (ICT) (Bajaj et al., 2008a) è, infatti, composto da tre differenti condizioni, che differiscono per le risorse esecutive necessarie. Se il controllo esecutivo è il fattore chiave nel determinare il deterioramento cognitivo osservato nei diversi compiti, allora l'effetto dell'età sulla performance all'ICT dovrebbe essere tanto maggiore quanto più elevato è il grado di controllo esecutivo richiesto. Inoltre, l'ICT ha permesso di studiare le alterazioni legate all'età negli ERP associati ai differenti meccanismi che compongono il controllo esecutivo, ovverosia l'aggiornamento nella working memory, l'updating e l'inibizione (Miyake et al., 2000).

I due studi saranno qui sotto descritti in dettaglio:

Esperimento 1: Meccanismi ERP sottostanti alle alterazioni, legate all'età, nella memoria prospettica basata sul tempo

Esiste un generale consenso, tra gli studi sulla MP, riguardo all'effetto deleterio che ha l'invecchiamento sulle prestazioni in compiti di MP basata sul tempo (Bastin & Meulemans, 2002; McDaniel & Einstein, 1992; Park et al., 1997; vedere anche Henry, MacLeod, Phillips, & Crawford, 2004, per una rassegna).

Secondo la teoria di Craik (1986), poiché nei compiti di MP non ci sono espliciti suggerimenti dall'ambiente che aiutano il recupero dell'intenzione, gli individui necessiterebbero di un maggior reclutamento di processi attenzionali e auto-iniziati per recuperare le intenzioni. Dato che l'invecchiamento è associato ad una riduzione nella disponibilità di tali risorse attenzioni, ciò determinerebbe un'alterazione nella prestazione dei compiti di MP negli individui più anziani.

Dall'altra parte, secondo la teoria del controllo cognitivo (o anche detta "ipotesi del mantenimento degli obiettivi"; Braver & West, 2008), gli anziani avrebbero delle difficoltà nella rappresentazione e nel mantenimento degli obiettivi nel corso del tempo. Nel caso della MP basata sul tempo, i deficit nel mantenere attivi gli obiettivi (cioè le intenzioni) porterebbe ad un fallimento nell'eseguire con successo l'azione intesa.

Sebbene un elevato numero di studi abbia esaminato come la MP basata sul tempo declini con l'età, tuttavia nessuno studio si è mai occupato finora di indagare l'attività neurale alla base di tale declino. Per tale motivo, il presente studio ha avuto lo scopo di esplorare le alterazioni legate all'età dei meccanismi elettrofisiologici alla base della MP basata sul tempo.

A tal fine, gli ERP associati ad un compito detto ongoing (i.e., un compito eseguito simultaneamente al compito prospettico) sono stati analizzati in 18 anziani e di 15 giovani e sono stati confrontati tra due diversi blocchi: il blocco di baseline e il blocco prospettico. Nel blocco di baseline veniva chiesto ai partecipanti di eseguire solamente il compito ongoing, mentre nel blocco prospettico si chiedeva di eseguire, assieme al compito ongoing, anche il compito di MP. Il compito ongoing consisteva nel valutare, all'interno di stringhe di cinque lettere, se le lettere in seconda e quarta posizione fossero uguali o diverse premendo con la mano destra uno di due possibili tasti. Nel compito di MP basata sul tempo, ai partecipanti era richiesto di premere un tasto ogni 5 minuti a partire dall'inizio del blocco prospettico. Per aiutarli nella stima del tempo, era stata data loro la

possibilità di controllare l'orologio (che sarebbe comparso sullo schermo qualora avessero premuto un ulteriore tasto). Gli ERP analizzati erano elicitati dalla comparsa dello stimolo ongoing (i.e., la stringa di lettere). I TR, l'accuratezza e gli ERP nelle prove ongoing sono stati analizzati confrontando il blocco di baseline e quello prospettico, sia nei giovani che negli anziani. Inoltre sono stati analizzati sia la percentuale di accuratezza nel compito prospettico che il numero di controlli dell'orologio.

Per quanto riguarda i risultati comportamentali, gli anziani mostravano una percentuale di accuratezza inferiore nel compito prospettico rispetto ai giovani. Inoltre gli anziani hanno mostrato un aumento dei TR al compito ongoing rispetto ai giovani, sia nella baseline che nel blocco prospettico.

A livello di dati elettrofisiologici, i giovani hanno mostrato delle modulazioni positive e sostenute degli ERP elicitati dagli stimoli ongoing dovute all'aggiunta del compito prospettico, che erano espresse maggiormente sopra le regioni frontali e prefrontali. Tali modulazioni riflettevano il carico nel mantenere le intenzioni attive in memoria, come recentemente suggerito (Cona et al., in press; West et al., 2011). Dall'altra parte, negli anziani, tali modulazioni erano maggiormente espresse sopra le regioni posteriori. È infatti interessante notare che i giovani, ma non gli anziani, mostravano una maggiore positività degli ERP nel blocco prospettico rispetto alla baseline a livello di siti frontopolari. Ad un primo sguardo, l'assenza della modulazione prefrontale negli anziani sembra riflettere la loro difficoltà nel mantenere in memoria le intenzioni prospettiche, in accordo con la teoria del controllo cognitivo (Braver & West, 2008). Tuttavia, l'analisi delle differenze ERP tra i due gruppi (già nella baseline) ha permesso di comprendere meglio quale fosse il meccanismo responsabile di questo peggioramento nella performance prospettica. Infatti nel blocco di baseline, se confrontati con i giovani, gli anziani mostravano una P300 meno ampia sopra le regioni parietali, e più ampia sopra le regioni prefrontali. L'anteriorizzazione della P300 negli anziani è un fenomeno già ben documentato in letteratura (Daffner et al., 2006; 2011) e sembra indicare il reclutamento di un maggior numero di risorse per compensare le difficoltà nell'eseguire il compito ongoing.

In generale, tali risultati suggeriscono che gli anziani hanno difficoltà già nel blocco di baseline, e che affrontano tali difficoltà reclutando risorse frontali addizionali (come indicato dall'anteriorizzazione della P300). Se troppe risorse sono reclutate per eseguire il compito ongoing, allora ne rimarrebbero meno per mantenere adeguatamente le intenzioni in memoria e ciò determinerebbe una performance peggiore al compito prospettico.

Sembra quindi più ragionevole assumere che il declino nel controllo esecutivo, richiesto per mantenere le intenzioni in memoria, non sia la causa primaria dei cambiamenti nei compiti prospettici, ma piuttosto sia a sua volta la conseguenza di una minor disponibilità di risorse cognitive, come postulato nella teoria di Craik (1986).

Esperimento 2: Influenza dell'invecchiamento sugli ERP associati ai processi legati al controllo esecutivo

Secondo la teoria del controllo cognitivo (Braver & West, 2008), un declino del controllo esecutivo dovuto all'età produrrebbe deficit in quei compiti cognitivi che coinvolgono in misura maggiore proprio quella funzione. Al fine di studiare tale ipotesi, abbiamo utilizzato l'Inhibitory Control Task (ICT; Bajaj et al., 2008a). Durante l'ICT, una serie di lettere viene presentata, molto velocemente, una dopo l'altra. Nella prima parte del compito è richiesto di premere un tasto quando compare o la lettera X o la Y. Le prove in cui compaiono tali lettere vengono definite prove *Detect.* Nella seconda parte del compito è richiesto di premere il tasto solo quando la X e la Y si alternano (prove Go), ad esempio quando la X è preceduta da una Y, o vice versa, indipendentemente dalle lettere che vengono presentate tra le due lettere target. Quando le lettere X e Y si ripetono (ad esempio, una X è preceduta da un'altra X), allora è necessario inibire la risposta (prove Nogo). In tal modo, l'ICT include prove che richiedono un differente grado di controllo esecutivo per essere eseguite. Infatti, le prove *Detect* richiedono semplicemente di prestare attenzione selettiva e di rispondere a specifici stimoli, e coinvolgono per questo un basso grado di controllo esecutivo. Le prove *Go* implicano anche un processo di aggiornamento nella working memory. Infine, le prove *Nogo* richiedono il maggior carico di controllo esecutivo, coinvolgendo non solo un processo di aggiornamento ma anche l'inibizione di risposta. Sulla base della teoria del controllo cognitivo, le differenze tra giovani e anziani nella prestazione all'ICT dovrebbero essere minori nelle prove detect, intermedie nelle prove go e massime nelle prove nogo.

In aggiunta, questo studio aveva lo scopo di studiare l'effetto dell'età sui singoli processi che compongono il controllo esecutivo (Miyake et al., 2000). Per tale motivo, è stato studiato l'effetto dell'età sull'ampiezza e la latenza della P3b, della P3-nogo e della RON (reorienting negativity) che riflettono rispettivamente i processi di aggiornamento, inibizione e shifting. Al fine di dissociare meglio quali fossero le componenti ERP legate ai

differenti processi studiati, è stata condotta la partial least square (PLS) analisi. Diciassette giovani e sedici anziani hanno partecipato all'esperimento ed eseguito l'ICT. Contro le predizioni formulate, i dati comportamentali hanno rivelato come gli anziani avessero una performance peggiore rispetto ai giovani in tutti i tipi di prove, quindi dalle prove detect alle prove nogo. È importante notare che l'effetto dell'età non interagiva con il tipo di prova, ed era quindi indipendente dal grado di controllo esecutivo necessario per eseguire quella data prova. Ciò indica che il controllo esecutivo, quando inteso come costrutto unitario, non sembra essere il fattore elettivo responsabile dei deficit mostrati dagli anziani nell'ICT. In linea con i risultati comportamentali, gli anziani hanno mostrato un ritardo in tutte le componenti ERP indagate (P3b, N2, RON, P3-nogo), indipendentemente dal tipo di prova esaminata. Questo ritardo nella latenza degli ERP legato all'età sembra riflettere un generale rallentamento dei processi cognitivi. Tale idea offre supporto alla teoria di Salthouse (1996), la quale assume che il declino cognitivo legato all'età sia dovuto ad una generale riduzione nella velocità di elaborazione.

Un altro risultato rilevante consiste nel fatto che le componenti RON sono risultate particolarmente sensibili all'invecchiamento. Tali componenti, che riflettono lo shifting attenzionale (Berti et al., 2008), erano ritardate e meno ampie negli anziani rispetto ai giovani. Solamente uno studio finora ha indagato le alterazioni, legate all'età, a carico delle componenti RON, ma utilizzando un paradigma uditivo di distrazione (Horváth et al., 2009). In questo senso il presente studio ha esteso i risultati ottenuti nello studio di Horváth, suggerendo che un declino nello shift attenzionale non avviene solo dopo stimoli distraenti (come evidenziato da Horváth) ma anche dopo stimoli rilevanti per il compito. Sembra, infatti, che negli anziani il meccanismo di shifting dell'attenzione sia più lento e dispendioso, probabilmente a causa del fatto che essi sono ancora occupati ad elaborare lo stimolo precedente.

Riassumendo, i dati elettrofisiologici e comportamentali convergono nel rivelare che il peggioramento nei compiti cognitivi associato all'invecchiamento potrebbe essere, almeno parzialmente, spiegabile da un rallentamento generale di elaborazione delle informazioni. Infatti, coerentemente con le conclusioni formulate nella rassegna di Verheagen (2011), una riduzione nella velocità dei processi sembra spiegare meglio i deficit cognitivi dell'anziano, rispetto ad un possibile deterioramento nel controllo esecutivo (quando inteso come processo unitario). Dall'altra parte, un sottoprocesso del controllo esecutivo, lo shifting attenzionale, sembra essere particolarmente sensibile all'età, e potrebbe quindi

rappresentare un possibile candidato per spiegare la molteplicità di deficit nell'anziano.

1° Parte: Conclusioni

Sebbene i presenti studi abbiano utilizzato differenti paradigmi e compiti, tuttavia convergono nel mostrare come il controllo esecutivo non giochi un ruolo cruciale nel determinare i deficit cognitivi evidenziati in questi compiti. Piuttosto, un declino nei processi più di base sembra essere il fattore chiave per spiegare la molteplicità dei deficit cognitivi nell'invecchiamento. In particolare, l'analisi degli ERP ha permesso di evidenziare che i cambiamenti legati all'età sono più probabilmente dovuti ad una riduzione: 1) nella disponibilità delle risorse cognitive, 2) nella velocità di elaborazione.

Le alterazioni elettrofisiologiche legate all'età sembrano interessare in misura maggiore le modulazioni ERP osservate a livello di siti prefrontali, ed sono particolarmente espresse in termini di ritardo delle latenze. È interessante notare la presenza di meccanismi compensatori negli anziani, riflessi in un aumento nell'ampiezza di diverse componenti (rispetto ai giovani). Ciò suggerisce che l'invecchiamento non solo implica un declino cognitivo e neurale, ma coinvolge anche risposte cognitive e neurali adattive.

2° PARTE: ALTERAZIONI COGNITIVE AND ELETTROFISIOLOGICHE ASSOCIATE ALL'ENCEFALOPATIA EPATICA MINIMA

L'encefalopatia epatica è una sindrome neuropsichiatrica che può presentarsi in pazienti con cirrosi epatica. Il rilevamento dei primi, seppur lievi, segni dell'encefalopatia epatica è estremamente importante. Questa iniziale e subclinica condizione, chiamata encefalopatia epatica minima (MHE; Ferenci et al., 1998) ha infatti un impatto sulla qualità della vita (Groeneweg et al., 1998; Zhou et al. 2009) e sull'abilità di guida (Wein et al., 2004). Inoltre, ha un valore prognostico negativo in relazione alla probabilità di sviluppare episodi di encefalopatia conclamata, nonché di morte (Amodio et al., 1999; Romero-Gomez et al., 2007). Il profilo della MHE è caratterizzato da alterazioni cognitive che coinvolgono processi quali l'attenzione selettiva, le funzioni esecutive, l'abilità visuo-motoria, la velocità di elaborazione, l'inibizione e la selezione di risposta (Amodio et al., 2005). La MHE causa anche una disfunzione cerebrale comunemente rilevabile sia dal rallentamento

dell'elettroencefalogramma (EEG) sia dal ritardo osservato nelle latenze degli ERP, tra cui la P300 (Amodio et al., 2005; Weissenborn et al., 2005). Quindi, quando possibile, la diagnosi di MHE dovrebbe essere preferibilmente basata su una combinazione di indici neuropsicologici/neurofisiologici.

L'Inhibitory Control Task (ICT) è stato recentemente proposto come un semplice strumento diagnostico per la MHE (Bajaj et al. 2007; 2008a). Tuttavia, la sua applicabilità a differenti popolazioni di pazienti con cirrosi, così come la sua relazione con altre misure di MHE necessitano di essere confermate. Per tali motivi, è stato condotto un esperimento (Esperimento 3) che aveva lo scopo di valutare la specificità e la sensibilità dell'ICT per la diagnosi della MHE.

L'Esperimento 4 si è invece focalizzato di indagare l'effetto della MHE sugli ERP elicitati dall'ICT, in modo tale da ottenere informazioni sulle alterazioni cognitive ed elettrofisiologiche caratteristiche della MHE.

A proposito delle alterazioni elettrofisiologiche legate alla MHE, un ulteriore esperimento (Esperimento 5) ha indagato la variabilità intra-individuale dei parametri della P300 (latenza e ampiezza) nei pazienti cirrotici con MHE. C'è un crescente interesse riguardo alla variabilità nella prestazione cognitiva (e.g., nei TR) nel campo delle neuroscienze cognitive (MacDonald et al., 2006) poiché la VII è stata largamente considerata un possibile indice comportamentale di meccanismi neurali compromessi (e.g., Hultsch et al., 2000). Tuttavia gli studi che hanno stabilito un legame tra la VII delle risposte comportamentali e quella delle risposte neurali sono ancora pochi. La MHE sembra un valido modello di patologia per studiare questa relazione poiché i pazienti con MHE mostrano un aumento nella variabilità dei TR (Elsass et al., 1985; Schiff et al., 2006).

Per tale motivo, nell'Esperimento 5, i parametri delle P300 misurati per ogni singola epoca, attraverso la tecnica di stima Bayesiana (D'Avanzo et al., 2011), sono stati esaminati per studiare il correlato elettrofisiologico della VII nella velocità di risposta. Inoltre sono stati esplorati i possibili cambiamenti nella relazione tra i parametri della P300 e dei TR che avvengono in pazienti con MHE.

Esperimenti 3 e 4: L'ICT come strumento adatto per rilevare le alterazioni cognitive ed elettrofisiologiche in pazienti con cirrosi epatica

Nell'**Esperimento 3**, 75 pazienti con cirrosi e 55 controlli sani hanno eseguito l'ICT presso due centri di riferimento per lo studio dell'encefalopatia epatica. I pazienti venivano valutati per la MHE attraverso il Psychometric Hepatic Encephalopathy Score (PHES) e le analisi spettrali dell'EEG. La performance alle prove go e nogo è stata comparata tra i due gruppi. I pazienti con cirrosi presentavano un maggior numero di errori (i.e., ***lures***) nelle prove nogo, e mostravano un'accuratezza peggiore anche nelle prove go, rispetto ai controlli. Tuttavia, il numero di lures era comparabile tra pazienti con e pazienti senza MHE. È importante notare come ci fosse una relazione inversa tra accuratezza nelle prove go e numero di errori, quando l'accuratezza nelle prove go era particolarmente bassa. Questo non è sorprendente: una bassa accuratezza alle prove go indica che molte di queste prove avevano una risposta mancante (infatti nelle prove go un errore consiste in una risposta mancante); tuttavia se un individuo commette tante risposte mancanti, allora è più probabile che "esegua" correttamente le prove nogo (le quali infatti prevedono una mancanza di risposta come 'risposta' corretta). In questo senso il numero basso di errori alle prove nogo è un fenomeno spurio. È stata quindi codificata una nuova variabile (weighted lures, o "lures pesati"), in cui il numero di lure veniva aggiustato per la percentuale di accuratezza nelle prove go. Tale variabile si è mostrata in grado di differenziare i pazienti con e i pazienti senza MHE. L'accuratezza nelle prove go si è rivelata comunque essere una valida misura anche quando veniva considerata da sola. Quindi, per rilevare segni di MHE, testare l'inibizione (lures) non sembra essere superiore rispetto al testare l'attenzione e l'aggiornamento nella working memory (accuratezza nelle prove go).

L'**Esperimento 4** ha permesso di studiare le alterazioni elettrofisiologiche legate alla cirrosi epatica ed evidenziate nelle prove che compongono l'ICT. In tale studio, sono stati analizzati gli ERP confrontando pazienti cirrotici con MHE (N=13), senza MHE (N=18) e individui di controllo (N=17). In particolare sono stati esaminati gli ERP elicitati dalle prove detect, go e nogo, in quanto possono essere un indice dei processi di attenzione selettiva, working memory e inibizione, rispettivamente. I dati sono stati inoltre analizzati attraverso l'analisi PLS, la cui efficacia nell'identificare variabili latenti è particolarmente adatta per dissociare i correlati ERP dei diversi processi. I risultati ottenuti dall'ANOVA e

dall'analisi PLS hanno mostrato alterazioni associate alla MHE che interessavano selettivamente gli ERP nelle prove detect. Specificatamente, queste erano rappresentate da una riduzione della P3a a livello di siti frontocentrali e da un ritardo della P3b. Poiché le prove detect coinvolgono principalmente processi attenzionali, le alterazioni evidenziate in tali prove potrebbero indicare un deterioramento delle abilità cognitive più di base, quali l'attenzione. Questo risultato corrobora la conclusione ottenuta nell'esperimento 3, che concerne l'appropriatezza di testare abilità più di base (come l'attenzione) prima, o assieme, alla valutazione delle abilità più di alto livello (i.e., l'inibizione). Il secondo principale, e inaspettato, risultato consiste nell'aumento (invece di una diminuzione) dell'ampiezza di diverse componenti (cioè la N2, la P3-nogo) in pazienti cirrotici senza MHE. Questi cambiamenti elettrofisiologici potrebbero essere un meccanismo compensatorio e riflettere l'allocazione di risorse esecutive addizionali per far fronte alle difficoltà nell'eseguire il compito (anche i pazienti senza MHE mostrano infatti una riduzione nella P3a, indice di deficit attenzionali).

Esperimento 5: La VII della P300 come indice per rilevare disfunzioni neurali in pazienti con cirrosi epatica

In pazienti con cirrosi, un'aumentata VII dei TR è già stata descritta, ed è stata considerata un possibile indice precoce di disfunzione cerebrale (Schiff et al., 2006). Sfortunatamente, la controparte neurale di questo fenomeno non è stata ancora dimostrata. Tuttavia, siccome una riduzione dell'ampiezza della P300 è stata osservata in questa popolazione di pazienti, allora è possibile ipotizzare che tale riduzione dipenda, almeno in parte, da un'aumentata variabilità delle latenze della P300 tra le singole epoche (come evidenziato per altre patologie, e.g., Hultsch et al., 2000). Per tali motivi, l'aumentata variabilità della P300, se evidenziata, potrebbe essere anch'essa un valido indice di disfunzione neurale. Inoltre, l'analisi della P300 per ogni singola epoca ha permesso di indagare la relazione tra i TR e i parametri (i.e., ampiezza e latenza) della P300, e comprendere come tale relazione cambi nel caso di patologie quali MHE.

L'EEG è stato misurato durante l'esecuzione di un compito di reazione di scelta (compito Simon) in 14 pazienti con MHE (diagnosticata sulla base di test e alterazioni all'EEG), 15 pazienti senza MHE e 14 individui sani di controlli. L'ampiezza e la latenza della P300, assieme alla loro rispettiva deviazione standard, sono state ottenute attraverso

un metodo non parametrico di stima bayesiana. La P300 è stata anche misurata con il classico metodo dell'averaging. Infine sono state analizzate la distribuzione dei TR e la sua relazione con i parametri della P300.

Nei pazienti con cirrosi, i TR erano più lenti e più variabili rispetto ai controlli. Un aumento nella variabilità della latenza della P300 è stato anche mostrato in tali pazienti. La regressione lineare multipla ha evidenziato come l'ampiezza della P300 – misurata con il metodo dell'averaging – era predetta sia dalla deviazione standard della latenza della P300, che dalla sua ampiezza (entrambe misurate con il metodo bayesiano). Ciò indica che una ridotta P300 nei pazienti con MHE potrebbe anche dipendere da un'aumentata variabilità nella latenza della stessa.

Inoltre, è stato mostrato come la latenza della P300 aumentava e l'ampiezza diminuiva all'aumentare dei TR nei controlli, ma non nei pazienti con MHE. Un altro segno di alterazione sembra quindi essere la più debole relazione tra parametri comportamentali e la P300, come osservato nei pazienti con MHE.

Riassumendo, il presente studio ha suggerito come in condizioni normali vi sia una stretta relazione tra TR e P300, e la P300 sia stabile tra le diverse prove. In contrasto, quando vi è una disfunzione cerebrale, come nel caso della MHE, la relazione tra i diversi parametri è meno forte, e le risposte neurali diventano più variabili.

2° Parte: Conclusioni

L'utilizzo dell'ICT ha fornito diverse evidenze riguardo ai marker cognitivi e neurali della MHE. Specificatamente, i pazienti con MHE hanno mostrato un rallentamento e un'attenuazione delle componenti della P300 nelle prove detect. Ciò sembra indicare deficit a carico dell'attenzione selettiva e sostenuta. Dall'altra parte, i pazienti senza MHE hanno evidenziato un aumento nelle ampiezze di alcune componenti (N2 e P3-nogo), che potrebbe riflettere un meccanismo neurale compensatorio.

Infine l'esperimento 5 ha evidenziato il profilo della P300 nei pazienti con cirrosi. Infatti, tali pazienti, e specialmente coloro che presentavano MHE, hanno mostrato un aumento nella variabilità della latenza della P300, che può aver contribuito alla riduzione della sua ampiezza.

CONCLUSIONI GENERALI

La tecnica dell'analisi ERP si è rivelata uno strumento utile per esplorare le alterazioni cognitive e neurali sottostanti sia all'invecchiamento sano sia a una condizione patologica, quale la MHE. Sono stati osservati alcuni pattern di alterazioni elettrofisiologiche comuni tra le persone anziane e pazienti con cirrosi epatica (e.g., rallentamento delle componenti ERP, aumento di alcune componenti, quali la N2). Tali alterazioni hanno evidenziato come 1) i deficit legati all'invecchiamento o alla MHE evidenziati in compiti cognitivi complessi sembrano dipendere da alterazioni a carico di meccanismi più di base (come deficit attentivi, o rallentamento nell'elaborazione degli stimoli); 2) l'attività neurale sia di individui anziani sia di pazienti senza MHE è similmente caratterizzata da meccanismi compensatori, reclutati per affrontare le difficoltà nell'eseguire i compiti.

GENERAL INTRODUCTION

The general purpose of the present dissertation is to explore the cognitive and electrophysiological changes occurring in normal aging (first part of the thesis) and in a particular type of brain disease, called Minimal Hepatic Encephalopathy (second part).

It is well known that aging is accompanied by a decline in a wide number of cognitive domains, including episodic memory, working memory, problem solving and spatial abilities (e.g. Hedden & Gabriel, 2004, for an overview). A great challenge in research on cognitive aging is to identify a potential common and unifying factor that might account for this plurality of age-related deficits. Some explanatory factors that have been proposed were the reduction of attentional resources (Craik & Bosman, 1992; Craik, 1983), or the general slowing in information processing (i.e., 'The processing-speed theory'; Salthouse, 1996). In Chapter 1 of the present thesis, the main theories of aging are described in detail in order to provide a picture of the most widely accepted views concerning the explanatory mechanisms of age-related cognitive decline.

Interestingly, a recent field of research focused the attention towards the dysregulation of executive control as potential mediator for age-related deficits, likely associated with changes in the prefrontal cortex (Braver & West, 2008; Raz, 2000; West, 1996). In particular, a group of theories, which are clustered in this thesis under the name of *'Theory of cognitive control'* (Braver et al., 2001; Braver & Barch, 2002; Braver and West, 2008), assumes that older adults have deficits in a particular aspect of executive control, namely in the ability to represent, maintain, and update task goal information in working memory. According to the theory of cognitive control (also called "goal maintenance account"; Braver & West, 2008), such age-related difficulties in the goal maintenance would produce decrements in several cognitive situations, and especially in those cognitive tasks that are particularly demanding with respect to this ability.

In light of this theory, two studies (Experiment 1 and Experiment 2) were designed to explore the possible role of executive control in determining age-related cognitive differences.

In Experiment 1, the performance and the event-related potentials (ERPs) elicited during a prospective memory (PM) task were compared between a group of younger and older adults (Chapter 2). The choice to study PM was driven by the fact that it is particularly suited to test the predictions made by the theory of cognitive control. PM

consists in remembering to execute an intended action in the future. A successful PM accomplishment entails that the intention to perform is maintained in memory until the conditions for performing the action are satisfied (Einstein & McDaniel, 1990). The prominent role of goal maintenance (i.e., the intentions) in PM tasks suggests that this would be a domain strongly affected by aging, according to the theory of cognitive control (Braver & West, 2008). In Chapter 2, this research is illustrated (Paragraph 2.4). Furthermore, it is described the features, the models and the electrophysiological correlates of prospective memory, as well as the studies concerning the effect of aging on PM performance (Paragraphs 2.1-2.3).

Experiment 2 was designed to explore the effect of aging on the specific sub-processes of executive control. Indeed, executive control has been conceptualized not only as a unitary function (e.g., de Frias, Dixon, & Strauss, 2006) but also as composed of three independent, although correlated, sub-processes: shifting (or switching) between tasks or mental sets, updating information in working memory, and inhibition of prepotent responses (Miyake, Friedman, Emerson, Witzki, Howerter, & Wager, 2000). In Experiment 2, a revised version of go/nogo paradigm – the Inhibitory Control Task (ICT) – was adopted (Garavan, Ross, & Stein, 1999). In addition, the ERP measures elicited by this task were compared in younger and older adults. The ICT, which comprises trials that require the updating, switching and inhibition processes, was particular suited to investigate executive control, especially in conjunction with the excellent temporal resolution of the ERPs. Thus, the effect of aging was explored on the ERPs elicited by ICT trials and related to each one of these processes. This study allowed us to better identify which, among the executive-control processes, was particularly sensitive to aging.

In Chapter 3, the aforementioned study is described (Experiment 2, Paragraph 3.4). Furthermore, It is provided a description about cognitive and electrophysiological features of inhibition, updating and shifting, and the main findings concerning the effect of aging on these processes (Paragraphs 3.1 - 3.3).

The second part of the thesis focuses on minimal hepatic encephalopathy (MHE). MHE refers to subtle alterations of cognitive functions, electrophysiological parameters and cerebral neurochemical/neurotransmitter homeostasis, frequently observed in patients with cirrhosis (Ferenci et al., 2002). The detection of MHE is a relevant health issue because of its impact on survival probability and quality of life, as well as its prognostic value on the occurrence of overt hepatic encephalopathy (Amodio et al., 2010). Nevertheless, the

cognitive and electrophysiological markers of this condition have been poorly investigated.

In two experiments of the present thesis, the ICT was employed to investigate the cognitive alterations (Experiment 3) and the electrophysiological counterparts (Experiment 4) associated with MHE. Indeed the ICT was recently proposed as a useful tool for the diagnosis of MHE (Bajaj et al., 2008a). The aim of Experiment 3 (Paragraph 4.3) was to assess the efficacy of ICT in detecting MHE by verifying the specificity and sensitivity of the task, and its relation with the neuropsychological and electrophysiological measures most commonly used for the diagnosis of MHE. In Experiment 4 (Paragraph 4.4), the ERPs elicited by ICT trials were examined in cirrhotic patients with MHE, in cirrhotic patients with no signs of MHE and in healthy controls. Since ICT trials require a plurality of cognitive processes, the study of the ERPs elicited by these trials would provide an overview of the cognitive and electrophysiological changes associated with MHE.

Finally, the last experiment (Experiment 5, Paragraph 4.5) was designed to investigate the differences in intra-individual variability (IIV) of RTs and of P300 parameters associated with MHE. The IIV of RTs has been object of study in a multitude of researches and has been proposed to be an index of brain dysfunction (Hultsch, MacDonald, Hunter, Levy-Bencheton & Strauss, 2000). On the other hand, the IIV of the ERPs has been poorly investigated (e.g., Fjell & Walhovd, 2007; Fjell, Rosquista, & Walhovd, 2008), probably because of the intrinsic limitations of the methods used for estimating the ERPs (i.e., the average of the sweeps). In Experiment 5, a new method based on the Bayesian single-trial estimation technique was used to obtain a measure of the IIV of the P300 parameters (latency and amplitude) under normal conditions and MHE. Furthermore, the extraction of single-trial parameters allowed to explore the relationship between RTs and P300 parameters, and hence to better understand the functional meaning of P300.

In Chapter 4, the neuropsychological and neurophysiological profile of hepatic encephalopathy and of its subclinical expression (the MHE) are described in detail (Paragraphs 4.1 and 4.2). In the same chapter, the three experiments are reported (in Paragraphs 4.3, 4.4, 4.5, respectively).

PART I:

Cognitive and Electroencephalographic Markers of Healthy Aging

CHAPTER 1

THEORIES OF AGING

1.1 BASIC COGNITIVE CHANGES IN AGING: AN OVERVIEW

Aging is usually associated with a change in a wide number of domains, both biological and psychological. A pessimistic view about the cognitive functions of elderly adults has been expressed for thousands of years. One example is the thought reported in the Republic by Plato (ca. 360 BC) who said that " . . . a man when he grows old . . . can no more learn much than he can run much." Moreover, in a relatively recent time (1890), even William James, the father of American psychology, wrote in the Principles of Psychology: "Outside of their own business, the ideas gained by men before they are twenty-five are practically the only ideas they shall have in their lives. They cannot get anything new. Disinterested curiosity is past, the cognitive grooves and channels set, the power of assimilation gone. . . . Whatever individual exceptions might be cited to these are of the sort that 'prove the rule.' "

More optimistic views about cognitive aging have been recently pointed out, highlighting that only some of the cognitive abilities decline with aging, whereas others remain relatively stable across lifespan, or even increase with age (Park et al., 2002). Also the neuroscience studies found that brain of older people is not only characterized by decline in the neural efficiency but also by increased and compensatory cerebral activations (Hedden & Gabrieli, 2004; Reuter-Lorenz, 2002; Reuter-Lorenz & Park, 2010, for reviews).

Below it will be presented a general overview of the main features of cognitive aging, and will focus not only on age-related cognitive impairments but also on those cognitive functions spared.

The cognitive functions, or mechanisms, most affected by age are episodic memory, working memory, attention and processing speed. In an extensive study published in 1996, Park and collaborators took a cross-sectional sample of individuals with ages ranging from

20 to 90 years. Participants were tested across multiple cognitive domains. This work and its expansions (Park & Gutchess, 2000; Park et al., 2002) found widespread declines in working memory, reading span, mental fluidity, processing speed, and in other areas of cognition, as can be seen in Figure 1.1.

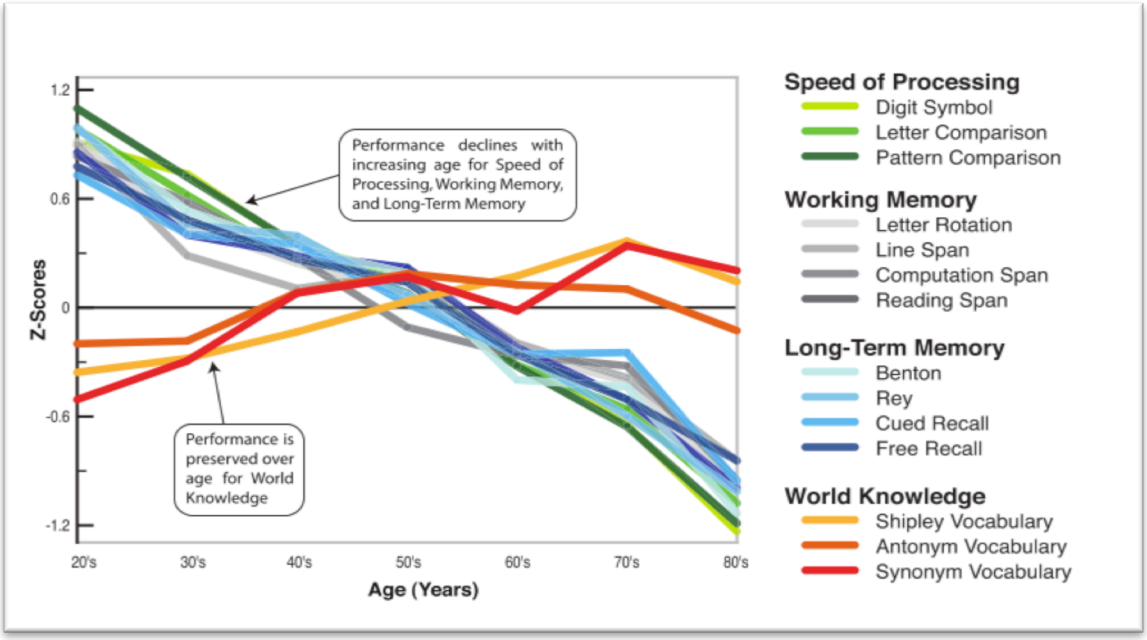

Figure 1.1 Changes of some cognitive functions across lifespan. Cross-sectional data showed age-related changes on measures of speed of processing, working memory, long-term memory, and world knowledge. Almost all measures of cognitive functions decline with age, except world knowledge, which appears even to have some improvement (adapted from Park et al., 2002).

Perception, even if interpreted by many researchers to be a precognitive function, also shows significant decline, mainly due to impairment of sensory abilities (Lindenberger & Baltes, 1994). Moreover, deficits at these early processing stages might influence the later cognitive stages of processing.

The cognitive domain that has probably received the greatest attention in aging is memory (for reviews, see Zacks, Hasher, & Li, 2000; Hedden & Park, 2001). Many elderly adults report an increased number of memory failures, and many studies tried to dissociate memory difficulties attributable to normal aging from those that are markers of pathological aging, particularly Alzheimer's disease.

Higher-level cognitive functions, including decision making and problem solving, seem to be also affected by age (e.g., Sanfey & Hastie, 2000; Schaie, 1996). These functions

seem to rely on more fundamental cognitive functions and, therefore, generally show deficits to the extent that those basic functions deteriorate. Notably, these complex tasks are accomplished by means of a set of executive functions, which coordinate and manage the different components of these tasks. As it will be described later in this chapter, executive functions are considered to play a crucial role in determining age-related declines in a range of cognitive tasks (e.g., West, 1996).

It is noteworthy that not all the cognitive abilities decline. For example, the studies by Park cited above evidenced that semantic knowledge and verbal ability were two domains that actually show improvement with age (Park et al., 2000; 2002). The (relative) stability of semantic memory and knowledge until late in life suggests that life experiences might enhance knowledge, and that the combination of experience and knowledge might give rise to the "cognitive reserve" or the so called wisdom, which is often exhibited by elderly individuals (Baltes, Staudinger, Maercker, & Smith, 1995; Stern, 2009).

1.2 MAIN THEORIES OF COGNITIVE AGING

1.2.1 Sensory deficit theory

According to 'Sensory deficit theory', older adults' cognitive deficits reflect a general impairment in sensory processing (Lindenberger & Baltes, 1994). Indeed, older adults usually show deficits in sensory functioning, such as vision and auditory processing (Schneider & Pichora-Fuller, 2000, for a review). The main evidence supporting this theory consists of the study by Lindenberger and Baltes (1994) who collected extensive sensory, medical, cognitive and social measures from a large sample of older adults with a wide range of age (70 to 103 years). They reported strong correlations between cognitive and sensory measures. Moreover they showed that almost all the age-related variance in cognitive performances (e.g., reasoning, memory, speed of processing, world knowledge, verbal fluency) was explained by sensory functioning (visual and auditory acuity). An important evidence from these studies (Lienberger & Baltes, 1994, Baltes & Lienberger, 1997, Baltes & Smith, 1997) is that having high cognitive ability, or being highly educated, does not protect from age-related decline. Specifically, it resulted that socio-biographical variables (education, social class) did not moderate the effect of age, suggesting that older adults show age-related decline independently of the initial level of cognitive functioning. Nevertheless, this result does not imply that individuals with different educational/social/cognitive level will display the same age effects in their everyday life. Indeed, as shown by Cherry and Park (1993), more educated individuals are characterized by higher levels of cognitive resources. Therefore, despite the cognitive decline quite uniformly showed by all socioeconomics groups, social and cognitive variables are relevant to modulate the number of situations in which cognitive aging puts older adults at risk.

Different views were developed for explaining the link between sensory theory and brain mechanisms. According to a 'cascade view', degeneration of sensory organs might lead to sensory deficits and consequently, to cognitive decline; on the other hand, the 'common cause view' posited that both sensory and cognitive deficits are mediated by a widespread neural degeneration (Schneider & Pichora-Fuller, 2000). Finally, a recent theory argued that sensory impairment might reflect a decline in functioning of sensory cortices (Cabeza, Dolcos, Prince, Budde, & Nyberg, 2004; Grady et al., 1994). Since perception is mediated by the interaction between sensory bottom-up processing and

cognitive top-down processing, then impairments in the former might be compensated by greater recruitment of the latter. Given that top-down operations partially depend on activity in prefrontal cortex (PFC), cognitive compensation would be mediated by an increase of PFC activity, as observed in several neuroimaging studies (e.g., Cabeza et al., 2004; Grady et al., 1994).

1.2.2 The processing-speed theory

One of the most popular and developed theories on aging suggests that the fundamental mechanism able to account for age-related decline is a generalized, reduced speed in performing cognitive operations (for a review, see Sathouse, 1996). According to Salthouse (1996), there are two main mechanisms responsible for the relationship between age-related cognitive decline and speed of processing. The first one is the "limited time mechanism": when too much time is required to perform the early operations, the time available for later operations is restricted. The second one is the "simultaneity mechanism", suggesting that the products of early operations become irrelevant, or are lost, by the time that later operations are accomplished. Thus, aging is characterized by cognitive decline because older adults are slower in executing early stages composing complex cognitive tasks. As a consequence, they might never execute the later stages given that the products of earlier operations are no more available. This view is corroborated by evidence that processing speed is very powerful to explain age-related variance on a multitude of tasks (Salthouse, 1996).

Recently, Verhaeghen (2011) reported several meta-analyses on aging. He showed that, although other cognitive constructs are recently hypothesized to be better mechanisms to account for age-related decline (e.g., the cognitive control, Braver & West, 2008), speed of processing remains one of the best explanatory mechanism of the age-related variance, also in complex tasks. An important point highlighted by the processing speed theory is that the reduced speed of processing is global and has an impact on all the aspects of cognition, even in complex tasks apparently not so strongly related to processing speed (for example, reasoning, recall, etc.).

One possible neural mechanism for explaining age-related slowing is the white matter deterioration (Gunning-Dixon & Raz, 2000), as revealed by several studies that measured age-related variation of white matter volume (e.g., Sullivan & Pfefferbaum, 2006) and

microstructure (as assessed with diffusion tensor imaging [DTI], which measures white matter integrity; see Kennedy & Raz, 2009 for a recent review). Indeed, since the myelin sheath serves to increase the speed of neural transmission along axons, its age-related deterioration would lead to a slowing down of neural communication.

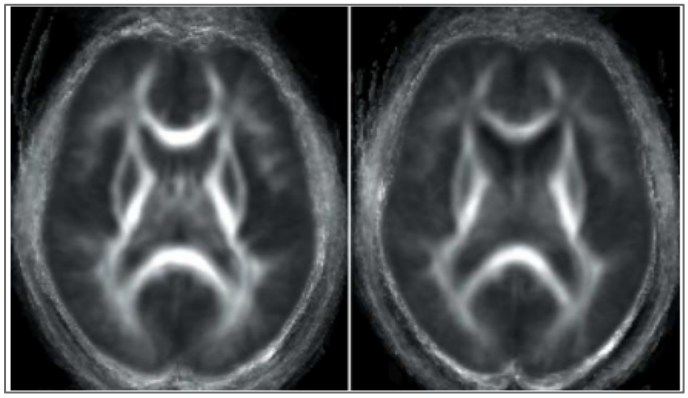

Figure 1.2 Deterioration of white matter in aging. Differences in white matter integrity between the brains of a young (left panel) and an old (right panel) individual (adapted from Hedden & Gabrieli, 2004).

1.2.3 Resources deficit theory

Craik and Byrd (1982) suggested that cognitive aging is related to a reduction in the amount of "processing resources", which results in a decline in cognitive demanding tasks. They claimed that decline in working memory (WM) capacity could explain the plurality of age-related deficits, especially in complex tasks. Working memory can be conceptualized as the amount of processing resources available and needed to retain and manipulate information. A classical example of task for measuring working memory is the computational span test, in which individuals are required to solve simple addition problems and simultaneously to remember the second number of each operation. Therefore in this kind of tasks it is required not only to retain information, but also to manipulate it. In line with 'resources deficit theory', older adults are usually shown to be impaired in these and similar types of tasks involving a high degree of processing resources.

Another aspect of the resources deficit theory is the "environmental support hypothesis" (Craik, 1983, 1986), which predicts that age-related differences should be reduced whenever the task provides environmental supports, namely when the task provides elements that decrease the processing demands of the memory task. The resources deficit

theory is also supported by evidence from younger adults' performance. Indeed, when the availability of processing resources is reduced during a task, younger adults show cognitive deficits that mime those displayed by older adults (e.g., Jennings & Jacoby, 1993).

Concerning the neural changes in aging, Craik (1983) originally argued that age-related reduction in processing resources was associated with a reduction in the efficacy of PFC functioning. This idea was confirmed by the fact that older adults show weaker activations in the PFC hemisphere that is typically involved in a given task as compared to younger adults. For example, in visuospatial working memory tasks – which imply activations in the right PFC – older adults showed weaker activations compared to younger adults in right PFC (Grady, McIntosh, Bookstein, Horwitz, Rapoport, & Haxby, 1998; Lamar, Yousem, & Resnick, 2004). Likewise, they usually show weaker activity in left PFC in episodic encoding tasks, which involve mainly the left PFC (Cabeza et al., 1997, Grady, McIntosh, Horwitz, Maisog, Ungerleider, Mentis, 1995; Grady, Bernstein, Beig, & Siegenthaler, 2002). This theory will be better described in the following Chapter, since it has been proposed to account for age-related deficits in a particular kind of memory, that is, prospective memory (see Chapter 2 for details).

1.2.4 Inhibition deficit theory

Hasher and Zacks (1998) attributed age-related cognitive deficits to a decline in the inhibitory control of working-memory materials. In other words, older adults have difficulties in focusing on relevant information and, at the same time, in inhibiting attention to irrelevant contents. Specifically, Hasher and Zacks suggested that the inability of older adults to inhibit goal-irrelevant information permits the entrance into WM of this information, leaving no more space for relevant information. In this way, the resulting reduced WM capacity would impair the operations inside WM, such as encoding and retrieving episodic information (for a review, Zacks, Hasher, & Li, 2000). Brain imaging researches documented specific age-related impairment in inhibitory control. For example, in a task of item recognition, older adults resulted more vulnerable than young adults to the interference exerted by distracting items, as shown by Gazzaley, Cooney, Rissman and D'Esposito (2005). Specifically, older and younger adults showed equivalent activations for the to-be-remembered items, but older adults displayed more distractor-related brain

activity as compared to younger adults. Such latter activity was inversely correlated with memory performance.

The inhibition deficit theory also suggested that older adults have difficulties in deleting no-longer relevant information, as evidenced in the greater proactive interference respect to younger adults (PI, that is difficulty in processing and learning new information because of already existing information) (Lustig, May, & Hasher, 2001). Interestingly, greater PI in older individuals is related to an impaired activation in a region of left inferior frontal gyrus that has been specifically associated with interference control (Jonides, Marshuetz, Smith, Reuter-Lorenz, Keoppe, Hartley, 2000). Age-related deficits in inhibitory control will be described in more detailed in Chapter 3 of the present thesis.

1.2.5 Theory of Cognitive Control

The Theory of Cognitive Control is a recent theoretical framework that encompasses various and updated versions of Braver and collaborators' theories, including the 'theory of cognitive control' (Braver & Barch, 2002), the 'context processing account' (Braver, Satpute, Keys, Racine, & Barch, 2005), the 'goal maintenance account' (Braver & West, 2008) and the 'dual mechanisms of control theory' (DMC, Braver, Gray & Burgess, 2007; Braver, Paxton, Locke & Barch, 2009). The common element of these theories is the key role of executive control in determining age-related changes. Moreover the alterations in PFC activity and in dopamine (DA) system are shown to be the crucial linkage between the age-related neurobiological changes and the behavioural and cognitive changes (Braver & Barch, 2002). Executive control is referred to as the ability to internal represent, maintain and update the information in order to exert control over thoughts and behaviour (Braver, Cohen & Barch, 2002). Older adults seem to have a decline in such ability, and specifically in actively representing and maintaining goal information over time (Braver & Barch, 2002). According to the theory of cognitive control, older adults should show the greatest difficulties under tasks in which: a) goal representations need to be maintained in WM over time in order to bias task-appropriate responses; b) goal representations are kept in mind as a template in order to enhance processing of low discriminable stimuli or actions; c) goal representations must be utilized to top-down suppress dominant but irrelevant features processing or to inhibit inappropriate responses (Braver & West, 2008). For example, in Stroop tasks (which involve naming the ink color of color-named words, e.g., the word

GREEN in red ink), the goal information provided by the task instructions must be continuously maintained (i.e., remembering to respond to ink color) in order to bias attentional allocation and, consequently, response selection from the word name to the ink color dimension. Several studies showed that older adults have difficulties in these, and other similar cognitive situations, such as the "go/nogo" paradigms, where goal representations are particularly important for successfully inhibiting inappropriate response and selecting the correct ones (e.g., Uttl & Graf, 1997; West & Alain, 2000; Paxton, Barch, Racine, & Braver, 2009). Braver and West (2008) reviewed how age-related changes, shown in different cognitive domains (such as, working memory, prospective memory, inhibitory control), could be easily accounted by a decline in the executive-control aspect of goal information maintenance. In the most updated view (i.e., DMC), Braver and collaborators identified two different types of executive control: the proactive versus reactive control (Braver et al., 2009). Proactive control is a preparatory mode in which goals are actively maintained in a sustained and anticipatory manner. It permits selective processing before the occurrence of imperative demanding cues. Reactive control occurs later, and is mobilized only as needed, such as after the presentation of a high-interference cue (Braver et al., 2009). Cognitive aging seems to be associated with inefficient proactive control, which would lead to greater reliance on reactive control (as respect to young adults).

Concerning the neural correlates of these two kinds of control, proactive control seems to be mediated by activity in PFC and by DA system. Specifically, sustained anticipatory activations of lateral PFC are related to goal information maintenance, whereas DA system mediates the access of goal information to PFC. On the other hand, reactive control depends on a more transient activity of lateral PFC, triggered by the detection of interference through the recruitment of areas related to conflict-monitoring, such as anterior cingulate cortex (ACC), or via associative connections, through posterior cortical regions (Braver et al., 2009). Age-related alterations in lateral PFC (West & Schwarb, 2006), in the regulation of DA system or in ACC were shown in several studies, corroborating the idea of a neuro-cognitive theory of aging.

Support for age-related differences in the proactive control comes from several studies that employed the AX-CPT paradigm (Braver et al., 2001; Braver et al., 2005; Paxton, Barch, Storandt, & Braver, 2006), which is a variant of the classic Continuous Performance Test (CPT; Rosvold, Mirsky, Sarason, Bransome, & Beck, 1956). In the AX-CPT

paradigm, participants are required to respond to an X-probe, but only when it follows an A-cue. Since target trials (AX) occur very frequently, two types of errors are usually shown and used for assessing maintaining and updating goal information (or, the proactive control). First, goal information updating is critical for inhibiting a response bias that occurs when a non-A-cue precedes an X-probe (‘‘BX’’ trials). Second, goal information maintaining produces an expectancy bias that triggers and facilitates target responses following an A-cue. Nevertheless, this expectancy bias might impair performance when a non-X-probe (‘‘AY’’ trials) follows the A-cue. Older adults showed a reversed pattern to young adults, which was indicative of a selective deficit in goal representation and maintenance (Braver et al., 2001; Braver et al., 2005; Paxton et al., 2006). Indeed, older adults had a worse performance than younger adults in both reaction times and accuracy on BX trials, due to a less efficient maintenance of the “goal” cue in memory, but performed better (than younger adults) on AY trials, where intact goal maintenance would cause an impairment in the performance.

The idea that a single construct, such as the executive control, might explain the plurality of deficits in aging is somehow reminiscent of the theory, discussed previously, that aging is associated with impairment in attentional demanding and self-initiated processes (Craik & Byrd, 1982). On the other hand, a recent meta-analysis showed how the role of executive control proposed for accounting age-related deficits is highly exaggerated. Executive control was shown not able to explain age-related variance in complex tasks over and beyond the effect mediated by processing speed (Verhaeghen, 2011). The role of executive control in mediating age-related cognitive changes will be explored in Chapter 3 and, with less extent, also in Chapter 2 of the present thesis.

1.2.6 CRUNCH model

Cognitive neuroscience has given rise to new models of cognitive aging that focus on functional or structural mechanisms to explain not only deficient but also preserved cognitive performance in older adults. One of the most prominent models is the *compensation-related utilization of neural circuits hypothesis* (CRUNCH, Reuter-Lorenz & Cappell, 2008), which was proposed to explain patterns of over-activation and under-activation in older adults. The CRUNCH model posits that the decline of neural efficiency might lead older adults to recruit more and different neural circuits than younger adults, in

order to meet task demands. This model is supported by several neuroimaging studies (e.g., Backman et al., 1997; Grady et al., 1992; see Park & Reuter-Lorenz, 2009, for a review). In general two different compensatory patterns were recognized. The first is the *posterior-anterior shift in aging* (PASA), which consists of an age-related decrease in occipital activity coupled with an age-related increase in PFC activity. Grady and colleagues (1995) were the first to report this pattern, comparing old and young adults on a face *versus* a place matching task. They found increased frontal activity but reduced occipital activity in older adults. Grady and colleagues claimed that such a pattern represented compensation for the failure to properly engage visual areas during encoding. The recruitment of these additional cortical areas allows older adults to perform at the same level of accuracy but with slower reaction times than young. The latter compensatory mechanism is the *hemispheric asymmetry reduction in old age* (HAROLD, Cabeza, 2002). This phenomenon, observed across several different cognitive domains, refers to a more bilateral (less asymmetric) pattern of activity in older adults then in young adults. A clear example of this different pattern of activity was provided by Reuter-Lorenz and colleagues (Reuter-Lorenz et al., 2000), who used PET to investigate age-related neural changes in verbal (letters) and spatial (dot position) encoding. Younger individuals showed left lateralized activation for the verbal task and right lateralized activation for the spatial one. Elderly participants had a bilateral pattern in both the two conditions. The HAROLD pattern was attributed to a compensatory mechanism, consistently with evidence that a more bilateral activity in older adults was positively correlated with successful cognitive performance (Reuter-Lorenz et al., 2000) and was found only in high-performing, and not in low-performing older adults (Cabeza, Anderson, Locantore, & McIntosh, 2002). The view that bilateral activation represents a compensatory mechanism has been supported by other studies (Rosen et al., 2002; Grady et al., 2002). An alternative account is that the more widespread activation pattern in older adults reflects a difficulty in recruiting specialized neural mechanisms (e.g., Li & Lindenberger, 1999; Logan, Sanders, Snyder, Morris, & Buckner, 2002).

Finally, the CRUNCH model is in line with the cognitive notion of "reserve", in that individuals with a bigger reserve (i.e., the whole of knowledge and competences acquired along the life) may face higher demanding tasks (Stern, 2009) making neural over-activation less likely at lower demanding tasks (e.g., Rypma, Eldreth, & Rebbechi, 2007). CRUNCH model is also in line with Scaffolding Theory of Aging and Cognition (STAC;

Reuter-Lorenz & Park, 2009 see below) since compensatory activations may provide scaffolding to support cognitive processes in aging.

In the experiments reported in this thesis, CRUNCH model was taken into account since it was able to explain some electrophysiological patterns, observed both in healthy aging and in pathology, which represented compensatory neural mechanisms.

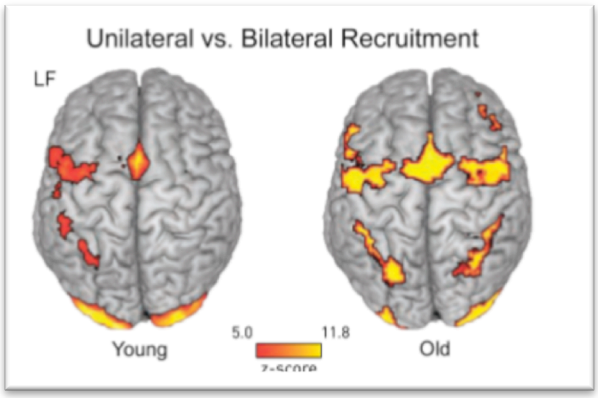

Figure 1.3 HAROLD pattern. Older adults show activations over the homologous area recruited by young adults (adapted from Schneider-Garces et al., 2010).

1.2.7 Scaffolding Theory of Aging and Cognition

The STAC model (Park & Reuter-Lorenz, 2009; Reuter-Lorenz & Park, 2010) is the most recent and integrative account among the theories reviewed above. The STAC model gives great importance to both neurocognitive decline as well as to neuroplasticity of aging brain. It claims that aging brain is characterized by a number of neural challenges to which it must overcome and adapt. Some of these challenges are morphological, including atrophy, amyloid deposition, white matter deterioration, and dopamine receptor depletion. Others are functional and include, for example, dedifferentiation (i.e., loss of brain regional specialization), decreased activation of MTL structures, and default network dysregulation. The default network consists of medial prefrontal, medial, and lateral parietal brain regions and is more active at rest than during cognitive tasks (Raichle et al., 2001). Dysregulation of default network in older individuals includes a less default suppression with greater task demand (Persson, Lustig, Nelson, & Reuter-Lorenz, 2007) and a less connectivity among default regions (e.g., Damoiseaux et al., 2008).

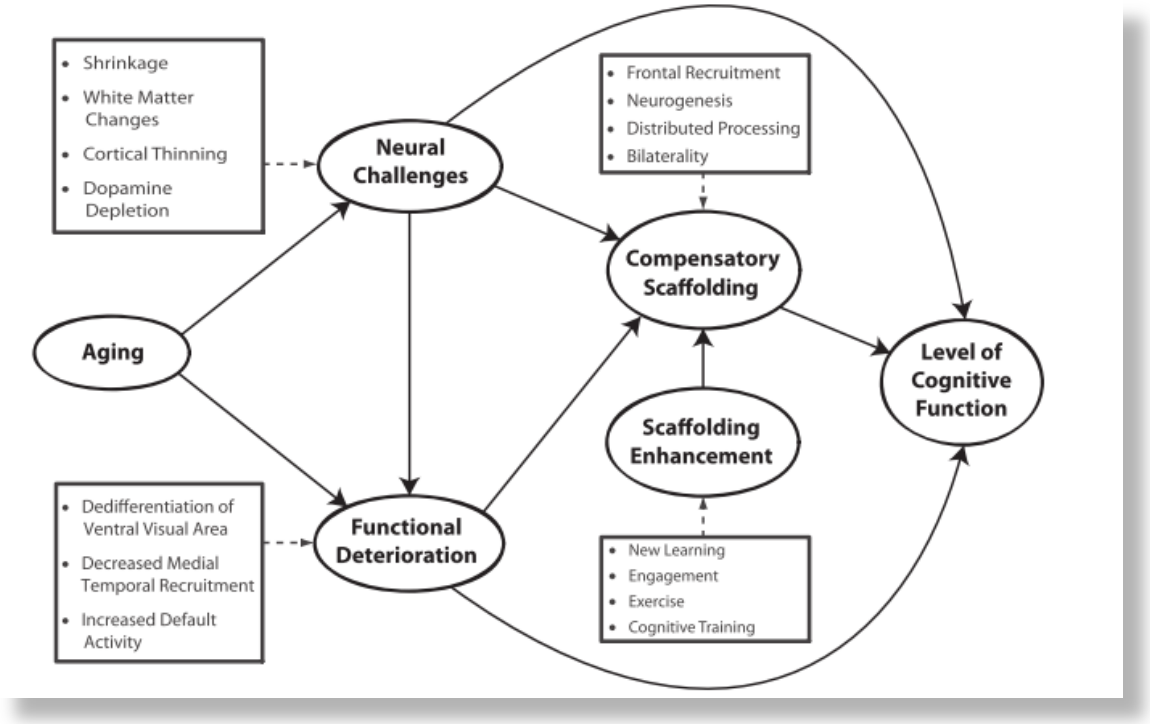

Figure 1.4 Graphic description of the Scaffolding Theory of Aging and Cognition (STAC) model adapted from Park and Reuter-Lorenz, 2009.

According to STAC, brain would overcome such neural alterations by forging alternative neural circuitries (i.e., scaffolds). Although scaffolds may operate less efficiently as compared to the networks of younger individuals, however they allow individuals to maintain a high (or at least adequate) level of cognitive functioning even at advanced ages. Scaffolds encompass patterns of over-activations, as reviewed above (e.g., PASA, HAROLD patterns), involving primarily the PFC, but also some areas within parietal, medio-temporal, and occipital regions. Compensatory scaffolding is strictly related to experiences. In light of this, new learning, cognitive training, active cognitive life and enhanced cardiovascular health might all mediate new neural scaffolding in order to maintain a high level of cognitive functioning. Furthermore, the model posits that mechanisms of neurogenesis, synaptogenesis, and angiogensis, even if less efficient in older than younger individuals, remain functional and help in forging alternative neural networks. This leads to the key idea that scaffolding is not a process beginning in old age, but rather, it concerns all the life span, given that individuals are always challenged by cognitive situations, which the brain must face. Thus, scaffolding is thought to be a lifelong process that is relied upon continually, but in an enhanced manner, in the older age.

CHAPTER 2

AGING AND PROSPECTIVE MEMORY

2.1 PROSPECTIVE MEMORY: FEATURES AND MODELS

One of the main aims of the present thesis is that to explore the role of age-related alterations of goals maintenance as potential factor to determine declines in cognitive performance of elderly individuals, as proposed by the theory of cognitive control (Braver & West, 2008). To this end, we chose to explore the effect of age on prospective memory (PM). Indeed, PM consists in remembering to accomplish some intentions in the future and implies that such intentions are maintained in memory even for a long period of time (Brandimonte et al., 1996). In the following paragraphs, the peculiar features of PM will be described and the most influential studies on the age effect on PM will be reviewed.

2.1.1 Introduction

How many times did you meet the following situations? After having sent an e-mail, you realized that you forgot to attach the file containing the results of one of your experiments. Or, after having prepared a delicious meal, the smell of burning remembered you that you forgot to take that out of the oven.

The errors cited above are only some examples of the failures in prospective memory (PM) and they demonstrate how relevant such ability is in everyday life. PM is commonly referred to the ability of remembering to perform intended actions at a particular time in the future (Brandimonte et al., 1996; Einstein & McDaniel, 1990). It is thought to be the result of a multicomponent process that includes the formation, maintaining, updating, and retrieval of an intention (Ellis & Freeman, 2008). Einstein and McDaniel (1990) distinguished three categories of PM tasks, depending on the kind of stimulus triggering

the intention retrieval: event-based PM tasks, time-based tasks and activity-based tasks (see also, Kvavilashvili & Ellis, 1996). In event-based PM tasks, individuals have to remember to perform an intended action when a particular event, the PM cue, occurs (e.g. remembering to put fuel in the car in the presence of a gas station). On the other hand, in time-based PM tasks, individuals have to remember to perform the intended action at a specified time or after a time interval (e.g., taking medication at noon or every twelve hours). A less studied type of PM task consists of the activity-based tasks, where the intended action has to be performed before or after finishing another activity as, for example, when taking a medication after breakfast.

Most laboratory studies used time-based, event-based or both of these types of intentions. In event-based laboratory paradigms, participants are usually engaged in an ongoing task, such as making lexical decisions, making picture or word ratings, answering questions, reading or taking a video tour of a town. When a specific event, the PM cue, appears (e.g., a word, face, concept, or category of elements), participants must execute overt responses to show that they have recollected the previously formed intention (e.g., Bisiacchi, Schiff, Ciccola, & Kliegel, 2009; Bisiacchi, Cona, Schiff, & Basso, 2011; Einstein, Holland, McDaniel, & Guynn, 1992; Ellis, Kvavilashvili, & Milne, 1999; Maylor, 1998; McDaniel, Robinson-Riegler, & Einstein, 1998). Therefore, event-based PM tasks are characterized by remembering to identify PM cues in the environment, which remind them to fulfil an intention. In contrast, in time-based laboratory paradigms, participants are engaged in similar ongoing tasks, but they are required to remember to complete intentions (e.g., pressing a key) at a particular moment, or after some duration has elapsed, such as remembering to perform an action every 5 minutes, or after 8 minutes (e.g., Einstein, McDaniel, Richardson, Guynn, & Cunfer, 1995; Hicks, Marsh, & Cook, 2005; Park, Hertzog, Kidder, Morrell, & Mayhorn, 1997; Mäntylä & Carelli, 2006). In time-based paradigms, participants are usually given the opportunity to check the clock in any moment of the task, for example by pressing a key and watching a digital clock appearing on the computer screen.

A common feature of time-based and event-based PM tasks is that individuals accomplish the intended actions while performing other ongoing activities and have to retrieve them without an explicit prompt from the environment that instigates them the recollection of the intended actions. Hence, PM has been often referred to as the ability to ‘‘remember to remember’’ and is composed of a retrospective and a prospective

component. The retrospective component allows people to retrieve the contents of the intention (i.e., retrieval the intended action and the associated context) from memory when the PM cue is recognized in the environment (Einstein & McDaniel, 1996). There is a relatively high overlap between processes that contribute to the retrospective component of PM and those belonging to other kinds of explicit episodic memory (Einstein & McDaniel, 1996; West & Krompinger, 2005). The processes related to prospective component are more closely mediated by executive control and underlie several phases of PM: the detection of PM cues in the environment, the coordination of the PM and the ongoing task, and monitoring the outcome of the intended action (Marsh, Hicks & Watson, 2002; West, 2011). As can be noticed, PM is not a single process, but involves different processes and is composed of several processing phases, which will be described in the following paragraph.

2.1.2 Phases of Prospective Memory

The first theoretical model (Hitch & Ferguson, 1991) that have conceptualized PM as a multi-phasic process comprising a phase of a) forming the intention, b) retrieving the intention from memory, and c) executing the intention at the appropriate time.

Successively, Kliegel and collaborators (Kliegel, Martin, McDaniel, & Einstein, 2002; see also Ellis, 1996) proposed a model that better disentangled the PM into four phases: (1) intention formation – reflecting the stage at which the intention is formed; (2) intention retention – the period during which the intention is maintained and retained while performing other ongoing activities (Ellis & Kvavilashvili, 2000); (3) intention initiation – the effective initiation of the intended action and (4) intention execution – when the action is executed in accordance with the previously formed plan (see Figure 2.1).

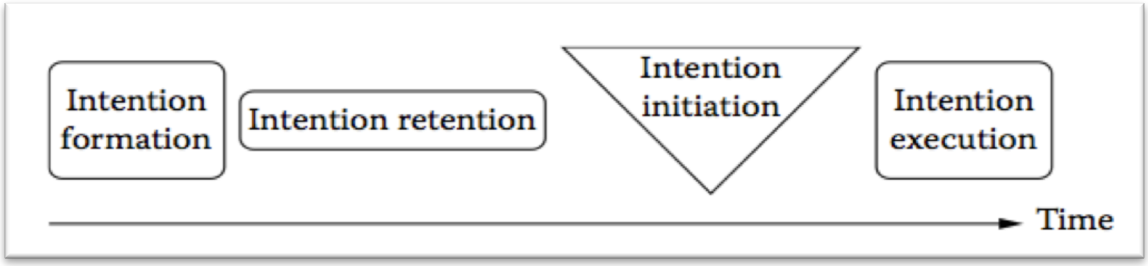

Figure 2.1 Phases of PM. Schematic description of the four phases composing prospective memory, as conceptualized by Kliegel and collaborators (adapted by Kliegel et al., 2002)

Distinct cognitive functions have been shown to underpin the different phases of PM. In general, intention formation, intention initiation, and intention execution phases can be assumed to involve specific executive functions, whereas the intention retention phase seems to be mainly related to retrospective component (Kliegel et al., 2002). More specifically, planning is the most influential function occurring during the intention formation phase. Indeed, performance observed in tests of planning, such as the Tower of London (Shallice, 1982) and the "Plan-a-Day" test (Funke & Krüger, 1993), was shown to correlate with PM performance at intention formation stage (Kliegel et al., 2002; Martin, Kliegel, & McDaniel, 2003). Intention retention seem to rely mainly upon retrospective storage capacity (Kliegel et al., 2002), whereas intention initiation phase is mediated by a number of executive functions, correlating with performance on tests of cognitive flexibility and monitoring. Likewise, performance at the intention execution phase correlates with performance on tests that require inhibition (e.g., the Wisconsin Card Sort test; Heaton, Chelune, Talley, Kay, & Curtis, 1993) and nonverbal fluency (5-points test; Lee, Strauss, Loring, & McLoskey, 1997), supporting the claim that flexibility is a fundamental cognitive aspect for the fulfilment of complex sets of intentions.

Concerning the event-based PM tasks, another model (Marsh, Hicks, Cook, Hansen, & Pallos, 2003) proposed that four processes subserve the execution of intended actions when a PM cue is encountered. These processes basically consist of PM cue detection and verification, intention retrieval, and coordination. The PM cue detection is the first operation to recognize the PM cue, whereas verification allows individuals to be sure that the PM cue meet all of the criteria required for triggering the PM intention. Intention retrieval mediates recollection of the intended action from memory. Finally, the intended action and the response relative to the ongoing task must be coordinated.

Taken together, these models clearly highlighted the multi-componential nature of PM, then it is reasonable to expect a different influence of aging on the distinct phases, or processes, as will be described below in Paragraph 2.2.

2.1.3 Models of Prospective Memory

Since in PM tasks there are no explicit prompts that instigate the intention retrieval, a central matter of debate is understanding how the intended action is usually retrieved at the appropriate moment. The majority of the studies investigated the processes underlying intention retrieval on event-based tasks, giving rise to opposing theories. Such theories ranged from viewing intention retrieval as relatively automatic (e.g., Automatic Associative Activation view, Noticing + Search view; Einstein & McDaniel, 1996; Guynn, McDaniel, & Einstein, 2001; McDaniel & Einstein, 2000; McDaniel, Guynn, Einstein, & Breneiser, 2003) to conceptualizing the retrieval as mediated by strategic processes (e.g., Preparatory Attentional and Memory processes theory; Burgess & Shallice, 1997; Ellis, 1996; McDaniel & Einstein, 2000; Shallice & Burgess, 1991; Smith & Bayen, 2004).

Specifically, two main models have received increasing support in recent years: the preparatory attentional and memory theory (PAM, Smith, 2003; Smith & Bayen, 2004) and the multiprocess view (MPV, McDaniel & Einstein, 2000; Einstein et al., 2005; Einstein & McDaniel, 2007), which assume a different involvement of strategic monitoring mechanisms in order to support the intention retrieval.

The PAM theory (Smith, 2003; Smith & Bayen, 2004) posits that intention retrieval is driven by preparatory strategic mechanisms that serve to monitor the environment for the occurrence of PM cues, and to compare the incoming cues with the intention-associated cue stored in memory. On the other hand, the multiprocess view (MPV, Einstein et al., 2005) assumes that intention retrieval is mediated by qualitatively different processes: strategic monitoring and spontaneous retrieval. The extent to which these processes are engaged varies according to the features of both the ongoing task and the PM cue. Specifically, in certain circumstances, for example when the PM cue is salient or prospective action is low demanding, the PM intentions previously formed can be automatically elicited by means of a 'spontaneous' retrieval mechanism. Otherwise, when these conditions are not satisfied, an attention-demanding monitoring process is required to check the presence of the PM cue in the environment (see below, for the details of the theories). Both the PAM and the MPV theories may be applied only for the event-based tasks, and cannot account for the time-based tasks where internal, but not external, PM cues are associated with the intended action.

A third model that specifically focuses on monitoring processes is the Strategic Monitoring view (Guynn, 2003; 2008), which has the advantage to make predictions also

concerning the time-based tasks. According to this model (Guynn, 2008), intention retrieval implies two independent resource-demanding processes: the retrieval mode and target checking. The retrieval mode is a continuous monitoring process and consists in maintaining active in memory the representation of prospective intention. Target checking is a more periodic process that intervenes by verifying the presence/absence of the PM cue in the environment (for event-based tasks) or by time monitoring (for time-based tasks).

Finally, the only model specifically focused on the mechanisms underlying the intention retrieval in time-based tasks is the 'Test-wait-test-exit model' (Harris &Wilkins, 1982; see also Kvavilashvili & Fisher, 2007). Based on this model, the rehearsals of time-based intentions (and the resulting time checks) usually happen prior to the appropriate time to remember and are periodically repeated until the successful execution of the intention. In the following section of the paragraph the different theories will be discussed in more detail.

- The Preparatory Attentional and Memory Processes (PAM) Theory (Smith, 2003; Smith & Bayen, 2004, 2005, 2006) proposes that intention retrieval is never automatic, but can only occur recruiting resource-demanding processes. The theory claims that successful PM performance is determined by a conjunction of preparatory attentional processes and retrospective memory processes. The preparatory attentional processes allow the recognition of a given event as a PM cue, by monitoring of the environment. In some cases, the attentional processes can operate outside of the focus of attention, thus without the awareness of the individual. On the other hand, memory processes promote the discrimination between PM cues and other (no-PM) events as well as the retrieval of the intended action. The idea that the preparatory attentional processes consume limited cognitive resources is driven by the fact that a successful performance on PM task is accompanied by some cost to the ongoing task (Smith, Hunt, McVay, & McConnell, 2007). The cost to the ongoing task is demonstrated by the decline in the ongoing task when a PM task is embedded, relative to blocks in which the ongoing task is performed alone. Smith (2003, Experiment 1) provided strong support for this theory, showing that participants were roughly 300 ms slower in performing a lexical decision task (as the ongoing task) when they were simultaneously performing a PM task respect when they were performing the lexical decision task alone. Moreover, Smith (2003) observed that individuals who showed a greater cost to the ongoing task had higher accuracy in PM

performance, thereby suggesting that monitoring is relevant for the intention retrieval. Cost to the ongoing task due to the addition of the PM task has been termed as the '*PM interference effect*' (Hicks et al., 2005; Marsh, Hicks, & Cook, 2006). PM interference effect has been found repeatedly, with other kinds of ongoing tasks (Smith & Bayen, 2004), and in other labs (e.g., Marsh, Hicks, Cook, Hansen, & Pallos, 2003; Einstein et al., 2005).

- The Multiprocess View (MPV; McDaniel & Einstein, 2000; Einstein et al., 2005; McDaniel & Einstein, 2007) argues that it is reasonably to believe that individual use both Strategic Monitoring and spontaneous retrieval in order to accomplish prospective intentions. First, because of the importance and prevalence of PM demands in everyday life, it would be more adaptive to have multiple processes for intention retrieval, which would in turn increase the chances that individuals will remember that intention under a variety of situations. Second, given that there is usually a remarkable delay between forming an intention and the appropriate moment to execute the intention (that is on the order of hours, days or even months), it seems maladaptive to have a system that is based exclusively on capacity consuming monitoring processes. Indeed, if individuals rely entirely on strategic monitoring, then the efficiency with which they performed the concurrent ongoing activities in everyday lives would be severely compromised. Third, the idea that individuals sometimes rely on spontaneous retrieval processes fits with Bargh and Chartrand's (1999) theory, according to which individuals prefer to use automatic processes since they have a limited capacity for executive control. Fourth, MPV is able to account for some apparently inconsistent results, for example the absence of the PM interference effect under several conditions (e.g., McDaniel et al., 2004). Based on MPV, the intended action is automatically retrieved from mind when: *i)* the intended action is low demanding, *ii)* the PM cue-intended action association is well learned, *iii)* the PM cue is a single and a salient event; *vi)* the PM cue is focal. Otherwise, when these conditions are not met, the retrieval of intended action is relied upon limited-capacity monitoring processes. In particular, Einstein and McDaniel argued that one of the important factors influencing the differential engagement of monitoring processes *versus* spontaneous retrieval is the '*focality'* of PM cues (Einstein & McDaniel, 2005; McDaniel & Einstein, 2000, 2007). A PM cue is focal when the features of the PM cue are easily extracted from the processing of the information relevant for the ongoing task, as when an individual is driving and he/she sees a gas station just in front of him/her. In this situation, the intention is

spontaneously retrieved (cf. Moscovitch, 1994). On the other hand, a PM cue is nonfocal when the ongoing activity does not encourage the processing of the PM cue, for example remembering to take a turn when the gas station is located somewhere not visible from him/her driving route. In this condition, attention needs to be allocated in order to strategically monitor for the presence of the PM cue.

Considered together, the PAM theory and MPV make similar predictions regarding the processes involved under some circumstances, but not in others.

- The Strategic Monitoring view (Guynn, 2003; 2008) assumes that strategic monitoring is composed of two mechanisms - the retrieval mode and target checking - and is involved in both the event-based and the time-based PM tasks. Retrieval mode is conceptualized as a "neurocognitive task set to treat stimuli (external or internal) as cues to retrieve intentions" (Guynn, 2003), or, in other words, as a sustained condition of readiness in order to respond to the incoming PM cues and, therefore, to appropriately execute the intention. The retrieval mode is also thought as a 'task set', thus costs to the ongoing task (i.e., the PM interference effect) would be predicted when individuals instantiate a retrieval mode or switch between retrieval modes (e.g., the retrieval modes of the PM and the ongoing task). In other words, the retrieval mode is based on maintaining the representation of intention active in memory. On the other side, target checking is a more intermittent mechanism; it occurs when the PM cue is expected and implies the allocation of attention to the stimuli in order to correctly verify whether or not they contain the PM cue. Given these assumptions, event-based and time-based PM tasks are similar in recruiting the retrieval mode mechanism, since they both require the intention to be maintained active in memory. On the other side, they differ in target checking: event-based PM tasks require monitoring of the environment for detecting the event target, whereas time-based PM tasks involve time monitoring by means of clock checks or an internal estimation of time throughout. Unfortunately, there is no existing model about how time-based intentions are successfully retrieved, except one dated model mainly based on intuition, called the test-wait-test-exit model (Harris & Wilkins, 1982).

- The test-wait-test-exit (TWTE) model (Harris & Wilkins, 1982) suggests that individuals intermittently test time (by checking the clock) to see whether the required time has come for executing the intended action. If the time is not correct, individuals wait for a period of time until another test seems appropriate. The exit of this loop happens when the critical time occurs and the intention is executed. Consistently with the TWTE model, the

majority of studies revealed that the overall pattern of clock checking frequency shows a J -shaped function (Einstein et al., 1995; Mäntylä, Carelli & Forman, 2007; Mäntylä, Del Missier & Nilsson, 2009; McFarland & Glisky, 2009; Tarantino, Cona, Bianchin, Bisiacchi, submitted). Indeed such studies evidenced that the number of clock checks is not constant throughout the task but increases as critical time is approaching. Interestingly, differences in the clock checking frequency were observed between young and older adults, as will be described later in this chapter (Paragraph 2.2.3).

2.1.4 Time-based versus event-based prospective memory tasks

The above-described models share the assumption that a successful performance in both the time-based and the event-based tasks must be mediated (at least under some circumstances, MPV; Einstein & McDaniel, 2005) by the recruitment of strategic monitoring processes. An index commonly used to quantify the engagement of monitoring processes is the PM interference effect, that is the decline of the ongoing performance when a PM task is added (Marsh, Hicks & Hancock, 2000; Marsh, Hicks, Cook, Hansen, & Pallos, 2003; Smith, 2003).

A largely unresolved issue in the literature on PM is which, between time-based and event-based tasks, produce greater PM interference effects. For example, is the performance of driving more negatively influenced by the intention to stop at the gas station (event-based intention) or by the intention to call a colleague in 10 min (time-based intention)? This question is object of interest to explore the specific characteristics and demands of engaging monitoring mechanisms in time-based versus event-based PM tasks.

The prevailing view of early works was that time-based PM tasks would exhibit a PM interference effect greater than event-based tasks since they would require a higher degree of self-initiated and controlled processes (Craik, 1986; Einstein, McDaniel, Richardson, Guynn & Cunfer, 1995). This claim was driven by the fact that in event-based PM tasks there are external events (i.e., the PM cues), which can be used as external triggers to recall the intentions. On the other hand, in time-based PM tasks there are no external cues that aid to elicit the to-be-performed action. In this case, individuals need to rely mainly upon their self-initiated processes to monitor the passage of the time and to execute the action (Einstein et al., 1995). Nevertheless, most of the studies found that event-based tasks had greater costs on ongoing task performance than time-based tasks (e.g., Hicks et al., 2005;

Marsh et al., 2006; Jäger & Kliegel, 2008, Tarantino et al., submitted; Park, Hertzog, Kidder, Morrell, & Mayhorn, 1997). For example, in the study by Jäger and Kliegel (2008) an n-back working memory task was used as the ongoing task, which consisted in evaluating whether the displayed picture matched the picture presented *n* stimuli back in the series. In the baseline block, n-back task was performed without any concurrent PM task. Whereas, in the experimental blocks, participants were required to concurrently execute the PM tasks, pressing a target key whenever a picture depicting an animal appeared (for event-based task) or every 5 minutes (for time-based task). In this latter case, participants were also given the opportunity to press the spacebar to monitor the time. The PM interference effect was found greater in the event-based task respect than in time-based tasks. Specifically, the addition of the event-based task (but not the time-based one) led to slower latencies in the n-back ongoing task, respect when the n-back was performed alone.

Park and collaborators (1997) speculated that the PM interference effect might be greater in event-based tasks because individuals need to pay constantly attention to the possible occurrence of the PM cue. In time-based tasks, individuals direct only sporadically the attention towards the PM task to monitor for when the crucial time is approaching. Hicks and collaborators (2005) extended Park's hypothesis suggesting that, in event-based tasks, the PM interference effect might be due to a trade off of the attentional allocation policy. Indeed in event-based PM tasks, attention needs to be allocated to process the same stimuli (e.g., the pictures in Kliegel's work) for two different purposes (e.g., to make the n-back ongoing task judgment and to execute the intention). The same is not true when individuals perform a time-based task, since in this case the stimuli are processed only for the ongoing task response.

Interestingly, Marsh and collaborators (2006) proved that PM interference disappeared in blocks where participants did not expect to find the event or time PM cues. The authors explained their results in the light of 'attentional allocation policies' (Marsh et al., 2005). According to the authors, at the time of PM instruction participants apply a strategy about how to manage the ongoing task and, consequently, how to distribute and divide the attentional resources. In this way, 'associating an event-based task with a future context can eliminate task interference until that context is reached' (Marsh et al., 2006, p. 1040). In line with such idea, the study by Tarantino and collaborators (submitted) found that predictability of the PM cue is a crucial factor in determining the extent to which monitoring attentional processes are engaged in the event-based and time-based PM tasks.

Specifically, in event-based PM tasks, the PM cue occurrence is not beyond the control of the individuals, then individuals engage a continuous monitoring process in order to be ready to detect the PM cue. On the contrary, in time-based tasks, in which the PM cue (i.e., the appropriate time) is intrinsically predictable, individuals are engaged in time monitoring (i.e., target checking) only periodically, as the occurrence of the PM cue approaches.

Summarizing, time-based and event-based PM tasks show qualitatively different monitoring mechanisms, more continuous and attention-meditated in event-based task, and more periodic and less demanding in the time-based task.

2.2 AGE-RELATED CHANGES IN PROSPECTIVE MEMORY

2.2.1 An overview of Aging and PM

An important object of interest in the literature on PM concerns the effect of aging on this ability. Indeed the implications of failures in PM can be dramatic under some circumstances, especially for older individuals for whom medication adherence, as example, represents often an important part of daily living (Insel, Morrow, Brewer, & Figueredo, 2006). The picture arisen from the studies is a ‘‘puzzle of inconsistent age-related declines in prospective memory’’ (McDaniel, Einstein, & Rendell, 2008), suggesting that multiple factors mediate the magnitude of age-related differences in PM tasks (as will be described in Paragraph 2.2.4). However, when taken together, this large number of studies show pronounced age-related deficits in the efficiency of PM, as revealed by a comprehensive analysis (Henry, MacLeod, Phillips, & Crawford, 2004; Uttl, 2008; 2011).

Originally, Craik (1986) argued that PM is characterized by a higher recruitment of self-initiated processes and the lowest extent of environmental support as compared to retrospective memory tasks (for example recognition or free recall). Indeed in PM tasks, the PM cue is not an explicit trigger to execute the intended action, but rather needs the interpretation either of an external event (i.e., PM event cue) or an internal thought. Therefore, larger age-related decrements in PM than in retrospective memory should be expected (e.g., Craik, 1986; Maylor, 1995; McDaniel & Einstein, 2000). In contrast, some meta-analyses indicated that age-related differences in PM tasks were comparable, or even lesser, than those found in retrospective memory tasks, especially when testing older adults in free recall tasks (Henry, et al., 2004; Uttl, 2011; but see Zeintl, Kliegel, & Hofer, 2007). In the same direction, in a meta-analysis of event-based PM, Kliegel, Jäger, and Phillips (2008) reported effect sizes that were larger for retrospective than for prospective memory. Although these results seem to be incongruent with Craik’s self-initiated processing theory, it may be that not all PM tasks are mediated by equivalent recruitment of self-initiated processing. Indeed the MPV model of event-based PM (McDaniel & Einstein, 2000) argued that PM performance can be supported by either self-initiated processes, such as strategically monitoring the environment for the presence of the PM cue, or by an automatic retrieval of the intended action. The extent to which the task depends on automatic processing *versus* controlled resource-demanding processing might account for

the mixed age effects in PM tasks (see Paragraph 2.1.3, for details on MPV).

Another matter of debate is if age differences in PM tasks reflect age decline mainly in the prospective or the retrospective component of PM. Some evidence indicated that aging might be associated with an impairment of processes related to the retrospective component of PM (Einstein et al., 1992; Zimmermann & Meier, 2006). For example, Cherry and collaborators (2001) showed that two indices of retrospective memory explained 68% of the age-related variance in PM tasks performance. Furthermore, it has been reported that age-related differences in PM tasks increased as a function of retrospective memory load implied in PM task, for example by increasing the number of PM cues to be remembered (Einstein, Holland, McDaniel, & Guynn, 1992). Finally, Zöllig and collaborators (2007) reported an increment in false alarms to stimuli that were similar to PM cues (i.e., lures) and in PM confusion errors in older adults relative to younger counterparts. These types of errors might be attributable to failures of the retrospective component of PM.

In contrast, other studies evidenced that aging had a stronger effect on processes related to prospective than retrospective components of PM (Cohen, West, & Craik, 2001; Smith & Bayen, 2004; West & Craik, 2001), even when the task implied relatively high retrospective demands (Cohen et al., 2001). Findings from the study by Smith and Bayen (2006), incorporating a mathematical model of the processes underpinning PM, are consistent with this claim. Specifically, Smith and Bayen showed that older adults were less likely to engage preparatory attentional processes that support the detection of PM cues than were younger adults, and that aging had little effect on retrospective component of PM. Moreover, a large number of studies indicated that age-related differences in executive functions and working memory capacity mediate the effects of aging on prospective memory (Bisiacchi, Tarantino, & Ciccola, 2007; McDaniel, Glisky, Rubin, Guynn, & Routhieaux, 1999; McFarland & Glisky, 2009). As an example, measures of these constructs were shown to account for 30% up to 100% of the age-related variance in PM tasks (Kliegel, Martin, & Moor, 2003; Salthouse, Berish, & Siedlecki, 2004; West & Craik, 2001).

In line with this view, Braver and West (2008) proposed that a decline in executive control might have a crucial role in determining age-related differences in PM tasks. According to their theory, called 'theory of cognitive control' or 'goal maintenance account' (Braver & Barch, 2002; Braver & West, 2008; see Chapter 1 for details on the theory), the

age-related decline in PM performance is due to difficulties in executive control, conceptualized as the ability to maintain and update goal-related contextual information to guide task performance. Indeed, failure to maintain the goals, or intentions in the case of PM tasks, seems to be related to a decline in efficiency of prefrontal cortex (PFC).

Summarizing, different theories tried to explain age-related deficits in PM tasks, from Craik's theory (1986), over McDaniel and Einstein' MPV view (2000), and finally to the Goal maintenance account (Braver & West, 2008). Nevertheless, understanding the key factor responsible for the age-related decline in PM is far from being a solved issue.

A review of the factors that were shown able to mediate the magnitude of the decline in PM performance will be presented in the following section, in order to provide detailed descriptions of the age effects on PM tasks.

2.2.2 Age effects on time-based and event-based PM tasks

Given that time-based and event-based PM tasks are mediated by different mechanisms, it is reasonable to assume that they might be differentially influenced by age. Although older adults generally have a worse performance on PM tasks than younger adults, age-related deficits are usually (but not always) more pronounced in time-based than in event-based tasks (d'Ydewalle, Bouckaert, & Brunfaut, 2001; Einstein et al., 1995; Gonneaud et al., 2011; Jäger & Kliegel, 2008). Specifically, there are conflicting findings for event-based PM tasks: many studies have found little or no age-related decline (Cherry et al., 2001; Einstein et al., 1992; 1995; Einstein & McDaniel, 1990), whereas other studies reported significant age-related impairments (Logie, Maylor, Della Sala, & Smith, 2004; Maylor, 1996, 1998; Park, Hertzog, Kidder, Morrell, & Mayhorn, 1997; West & Covell, 2001). In contrast, for time-based tasks, the studies converge toward a detrimental effect of age (d'Ydewalle, Bouckaert, & Brunfaut, 2001; Einstein et al., 1995; Jäger & Kliegel, 2008).

Researchers suggested that age-related decline is greater in time-based tasks because of the higher degree of controlled and self-initiated cognitive processes involved in these kinds of tasks as compared with event-based tasks (Bastin & Meulemans, 2002; Einstein et al., 1995). This idea is in line with Craik's theory (1986), according to which few environmental aids would lead to an increased use of self-initiated effortful processes, inducing in turn a decrease of cognitive efficiency in older adults. However, this

hypothesis is not supported by the study of d'Ydewalle, Luwel, and Brunfaut (1999), who reported a greater accuracy in time-based than in event-based task for older participants. The authors attributed this pattern of results to the decrease in speed of processing in adulthood and suggested that older adults are quite capable to successfully perform time-based tasks, if the timing constraints imposed by the task allow them to allocate sufficient time to time-monitoring. Moreover, a meta-analysis (Henry et al., 2004) observed that, within laboratory PM tasks, there were not significant differences between the size of the age effect on time-based (age effect = − .39) and event-based tasks (age effect = − .34).

The MPV (McDaniel & Einstein, 2000) might account for this apparent inconsistency across studies for event-based tasks, suggesting that the magnitude of age-related changes on event-based tasks is determined by the extent to which these tasks depend on automatic processing versus self-initiated controlled processing. This view indicates that the following aspects may enhance the controlled demands of PM tasks, leading to an increase of age-related deficits: (a) not salient PM cue, (b) a weak relation between the PM cue and the intended action, (c) nonfocal PM cue, or (d) a highly demanding ongoing task (see Paragraph 2.2.4, for a detailed description of these factors).

Another unsolved but relevant issue concerns whether the PM interference effect is differentially affected by aging between time-based and event-based tasks. PM interference effect might clarify whether older individuals show an enhanced cost on the ongoing task in order to perform PM tasks adequately, or on the same level, as the younger counterparts. Available data are mixed in this regard. Bastin and Meulemans (2002), Jäger and Kliegel (2008) and Park and collaborators (1997) did not find age differences in the PM interference effect in both the two PM tasks. In contrast, d'Ydewalle and collaborators (2001) reported that, as compared with younger adults, older adults showed a greater decline in ongoing task accuracy when a time-based but not an event-based task was performed. A study that have specifically investigated the age effect on event-based task (McDaniel et al., 2008) reported that older adults showed a greater PM interference effect than did younger counterparts when they had to monitor for nonfocal PM cues (but not for focal ones). Likewise to studies employing event-based tasks, also a study that focused on time-based tasks (Mäntylä et al., 2009) reported a greater PM interference effect for older adults than younger adults. Another study (Logie et al., 2004) reported the reverse pattern, with younger adults exhibiting a greater PM interference effect than older adults when either time-based or the event based tasks was added.

A way to better understand the mechanisms underpinning the age-related decline in time-based and event-based PM performance is that of identifying which cognitive functions can mediate such decline in the two PM tasks. Early studies showed a significant relationship between PM performance and other cognitive functions in older participants (Martin, et al., 2003; Park et al., 1997; West & Craik, 2001), or in both younger and older adults (Bisiacchi, et al., 2007; Cherry & LeCompte, 1999; Kidder, Park, Hertzog, & Morrell, 1997). Such correlations concerned working memory (Cherry & Le Compte, 1999; Kidder et al., 1997; Park et al., 1997; West & Craik, 2001), executive functions (Marsh & Hicks, 1998; Martin et al., 2003; West & Craik, 2001), processing speed (West & Craik, 2001), retrospective episodic memory (Cherry & LeCompte, 1999), and metamemory (Kliegel & Jäger, 2006; Mäntylä, 2003; Zeintl, Kliegel, Rast, & Zimprich, 2006). All these studies used event-based tasks, with the exception of Park and collaborators (1997) and Martin and collaborators (2003) who used both time-based and event-based tasks. Interesting, Kliegel, Ramuschkat, and Martin (2003) highlighted that time-based and event-based tasks relied upon different executive processes, with time-based requiring shifting, and event-based involving inhibition. A recent study (Gonneaud et al., 2011) showed that both common and distinct mechanisms mediate the effect of aging in PM performance on time-based and event-based tasks. Indeed the performance of older individuals was predicted by inhibition and processing speed in both the PM tasks. However, while event-based performance was mainly related to retrospective memory and binding processes, time-based performance was mainly mediated by inhibitory processes.

2.2.3 Age effects on time-based tasks: the role of Time Monitoring

While the results about the functions mediating age deficits in PM are far from being clear-cut, the relationship between time-based PM and time monitoring measures has been more consistently shown in older individuals (as well as in younger adults) (Einstein et al., 1995; Khan, Sharma, & Dixit, 2008; Mäntylä et al., 2009). Several studies have consistently reported, for both the two age groups, a relationship between time-based performance and clock checking frequency (Einstein et al., 1995; Khan et al., 2008; Mäntylä et al., 2009). Interestingly, an increase in the number of clock checks in the period just preceding the crucial time has been shown to determine an improvement in the PM performance (Kvavilashvili & Fisher, 2007).

Several studies evidenced that the number of clock checking was lower for older relative to younger adults, and that such effect was accentuated during the period just preceding a PM action (Einstein et al., 1995; Park et al., 1997). The authors suggested that the reduced number of clock checks in older adults could lead in turn to an impaired PM performance, as observed in these studies (Einstein et al., 1995; Park et al., 1997).

However, the findings obtained from two other studies (Logie et al., 2004; Maylor et al., 2002) highlighted a rather different pattern when considering the pattern of clock checks separately before failures in PM response or successes. Specifically, in the study by Maylor and collaborators (2002; Experiment 1), participants viewed a film (as ongoing task) for a successive recognition memory task and they were instructed to stop a clock every 3 minutes (time-based PM task). Young participants performed better than older participants in time-base PM task. The PM accuracy was associated with the frequency of clock checking. In particular, before successful PM responses, older participants checked the clock more often as compared to young participants, and clock checking was more frequent (and very similar across the groups) in the last period of the 3-minute time interval (see also Logie et al., 2004). On the other hand, before unsuccessful responses, older adults showed a flat monitoring function even in the last period of the 3-min interval. According to the authors, this pattern of results is consistent with the idea that momentary lapses of attention are responsible for time-based PM deficits in aging.

Mäntylä and collaborators (2009) showed a pattern of clock checks in older adults that was different as a function of the demands required for the ongoing task. Specifically, the frequency of clock checks increased across age in the low-load condition (i.e., listening to a short story), with older adults checking the clock more frequently than younger counterparts. This older adults' compensatory monitoring strategy allowed them to obtain the same level of PM performance shown by younger counterparts, but led in turn to an additional cost in ongoing task performance (see Paragraph 2.2.4, for the role of ongoing task in determining age effect in PM). On the other hand, when the ongoing tasks demands were high (i.e., a series of cognitive tasks), the older participants reduced their clock checking, and consequently had an impaired PM performance. A plausible explanation of this pattern of results is that older adults did not have attentional resources enough to adopt the same compensatory strategy as under the low ongoing task condition, which led to age-related decline in PM accuracy.

Taken together, these studies show 1) the importance of adopting a good strategy of

clock checking to have a successful performance in time-based tasks 2) age-related differences in time-based performance might be due to an inefficient use of these clock checking strategies.

2.2.4 Factors influencing the magnitude of age-related differences in PM tasks

It is clear from reading the paragraphs presented above that there are conflicting findings concerning the age effects on performance in PM tasks. In order to explain this picture of mixed results, different dimensions related to both the PM and ongoing tasks have been highlighted as relevant in determining the size and direction of age effects on PM performance. Specifically, the MPV suggested that the following variables may increase age-related deficit: (a) salience of PM cue, (b) strength of the relation between the PM cue and the intended action, (c) focality of PM cue, or (d) demands of the ongoing task (McDaniel & Einstein, 2000).

Moreover, a great difference in the age effect on PM performance has been found between PM tasks carried out in laboratory versus in naturalistic setting. Therefore, the present paragraph will describe the impact of the variables that most frequently have been identified as mediating age-related effects on PM tasks:

- *Naturalistic versus laboratory PM tasks*

As previously noted, older adults tend to perform worse in PM tasks as compared to younger adults, when they are tested in laboratory settings (Henry et al., 2004). On the other hand, it is quite surprising that older adults perform as well, or even better, than their younger counterparts, in PM tasks that are carried out in naturalistic settings. In naturalistic paradigms, PM tasks include indices artificially introduced by the experimenters inside of a naturalistic environment. The PM tasks consist, for example, in remembering to telephone the experimenters at a specific time over 5 days (Maylor, 1990); 2 weeks (Moscovitch, 1982); and 4 weeks (Devolder, Brigham, & Pressley, 1990); in sending the experimenter mail postcards (Patton & Meit, 1993); or to log the time on electronic organizers (Rendell & Thomson, 1993). Older adults were also reported to have a better PM performance in realistic settings, such as following medication schemes (Hertzog, Park, & Morrell, 2000; Park et al., 1999; Park & Kidder, 1996) and attending appointments (Martin, 1986).

Several authors tried to explain this age–PM paradox (e.g., Maylor, 1996; Rendell & Thomson, 1999). For example, Maylor (1996) suggested that, because of the more experience gained through real-world PM tasks across the life span, older adults have developed a greater number of compensatory strategies that would improve PM performance in naturalistic settings. The higher performance of older adults in naturalistic tasks has been also attributable to more experience with time management, generational differences in attitude to punctuality, fewer distractions, awareness of their memory's failures, or more efficient utilization of PM reminder aids (e.g., Dobbs & Reeves, 1996; Kvavilashvili, & Ellis, 2004; Logie et al., 2004; Rendell & Craik, 2000; Rendell & Thomson, 1999). However, current understanding of the role of motivation, memory aids, motivation, practice, and lifestyle in PM tasks is still poor, and require to be addressed through the use of more controlled manipulations in large-scale studies. The exploration of this paradox might also enhance theoretical models of PM and shed light on the importance of PM in everyday life.

- *Focal versus Nonfocal PM cues*

In their multiprocess view (MPV) of event-based PM, Einstein and McDaniel argued that one important factor modulating age effects in PM may be the focality of PM cues (Einstein & McDaniel, 2005; McDaniel & Einstein, 2000, 2007). A PM cue is *focal* when the features of the PM cue are easily extracted from the information relevant for the ongoing task (i.e., PM cues overlap with the information features relevant to execute the ongoing task). An example of focal PM situation occurs when you are driving and you see a gas station just in front of you. On the other hand, a PM cue is *nonfocal* when the ongoing activity does not encourage the processing of the PM cue, for example when the gas station is located somewhere not visible from your driving route. According to MPV, in focal PM cue condition, the intention is spontaneously retrieved whereas when the PM cue is nonfocal, attention needs to be allocated to strategically monitor for the presence of the PM cue.

In their meta-analysis, Kliegel and collaborators (2008) tested the importance of PM cue focality on age-related differences in PM event-based tasks. Representative laboratory examples of focal and nonfocal tasks are responding to the word 'tortoise' (focal PM cue) or to the syllable 'tor' (nonfocal PM cue), while being engaged in a lexical decision task as ongoing task (Einstein & McDaniel, 2005). Across all studies, their analysis revealed that

age-related declines were larger for nonfocal cues (d=0.72) than focal cues (d=0.54). This result is consistent with the MPV (McDaniel & Einstein, 2000) according to which age effect should increase for nonfocal than for focal PM cues, because controlled, self-initiated processes have to be engaged to a higher extent in order to screen the environment for nonfocal PM cues (Einstein & McDaniel, 2005; Rendell, Jensen, & Henry, 2007). However, this meta-analysis showed that age deficits occurred not only in nonfocal PM tasks but also in focal ones. This finding has implications for the MPV by pointing out that the view's stronger prediction has to be revised, namely, the prediction that age-related declines should not occur in focal PM tasks because such tasks are mediated by spontaneous (i.e., relatively automatic) retrieval processes.

Another recent meta-analysis conduced by Uttl (Uttl, 2011; see also, Uttl, 2008) examined this issue thought the use of more robust technique (e.g., modelling and data visualization, robust count methods) and taking into account several biases not considered in the previous meta-analyses (e.g., age confounds, ceiling effects, inclusion of vigilance tasks). In such work, Uttl reported that the size of age effect in PM tasks was large not only with nonfocal but also with focal PM cues, contradicting the MPV's idea that prospective remembering with focal cues, being automatic, is spared by aging.

- *Low-demanding versus high-demanding ongoing tasks*

A number of studies have shown that the nature of the ongoing task in which the PM task is embedded is relevant in determining the size of age-related differences in PM tasks (d'Ydewalle, 1995; d'Ydewalle et al., 1999; Martin & Schumann-Hengsteler, 2001; Rendell, McDaniel, Forbes, Einstein, 2007; West & Bowry, 2005). Indeed age effects typically increased if the cognitive demands of the ongoing task were high (Mäntylä et al., 2009; Maylor, 1995).

Logie and collaborators (2004) addressed this topic by using two kinds of ongoing tasks, which differed with respect to working memory load (see also Mayor et al., 2002). Specifically, participants were required to watch a film (low-demand condition) or execute arithmetic tasks (high-demand condition) and concurrently perform an event-based or a time-based task. These tasks consist in indicating when an animal occurred, or when 3 minutes had elapsed, respectively. Younger participants performed more successfully in both time- and event-based PM tasks than older counterparts, but only when the ongoing task was high demand. No differences were observed in the PM tasks between younger and

older adults when the ongoing task was demanding. Also Mäntylä and collaborators (2009), who focused on time-based tasks, reported a similar pattern of results. In the low-demanding conditions older adults produced similar levels of PM performance by increasing clock checking as respect to younger participants (see Paragraph 2.2.3). On the other hand, when the task demands were enhanced, as in the high-demanding condition, older adults were not able to check the clock frequently, which led in turn to a worse PM performance.

Another study (Bisiacchi et al., 2007), focusing on event-based PM task, showed that older individuals failed significantly more often in PM tasks, even in low-demanding ongoing conditions.

Finally, other factors responsible for mixed results on age-related decline in PM tasks are the typicality (Cherry et al., 2001; Mäntylä, 1993, 1994) and the salience (Einstein et al., 2000) of the PM cue, as well as the complexity of PM tasks, with high-strategic-demand PM tasks resulting in the largest age-related deficits (Henry et al., 2004; Martin et al., 2003).

2.3 AGE-RELATED CHANGES IN PM: ELECTROPHYSIOLOGICAL EVIDENCE

All the studies that have investigated the electrophysiological bases of PM focused on event-based PM tasks, except for one (Cona, Arcara, Tarantino & Bisiacchi, in press). As a consequence, the electrophysiological results described in this section will mainly concern the event-based PM. Within the electrophysiological literature of PM, two categories of event-related potentials (ERPs) are usually explored: the former comprises the ERPs elicited by the PM cues, which provide insight on the neural correlates of the distinct processes of prospective remembering that occur when a PM cue is encountered (West, 2011; for a review); the latter consists of the ERPs elicited by ongoing trials comparing them in two conditions, namely when the ongoing task is performed alone (i.e., baseline condition), and together with a concurrent PM task (prospective condition). This kind of ERPs reflects the PM load on ongoing task, and the engagement of strategic monitoring processes (Chen et al., 2007; 2009; Knight et al., 2010).

2.3.1 Age effects on ERPs associated with PM cues

As recently reviewed by West (2011), a number of studies identified the ERPs related to the different processes composing PM, such as the PM cue detection (N300), the retrieval of the intention (parietal old-new effect; FN400), and the configuration of the prospective response (prospective positivity). The effect of aging on these ERPs has been studied in order to understand the electrophysiological mechanisms underlying age-related alterations in event-based PM tasks (Mattli, Zöllig, & West, 2011; West & Bowry, 2005; West & Covell, 2001; West, Herndon, & Covell, 2003; Zöllig et al., 2007).

The N300 reflects a negativity, greater for PM cues than for ongoing trials, and expressed between 300 and 500 ms post-stimulus over the occipital–parietal sites of the scalp (West, 2007; West, Herndon, & Crewdson, 2001). The amplitude of the N300 is higher for PM hits (PM cues which receive a correct PM response) than for both PM misses (PM cues associated with a forgotten response) and ongoing activity trials (West, 2007; West & Krompinger, 2005; West & Ross-Munroe, 2002). This pattern of results might indicate that N300 reflects the detection of the PM cue in the environment. The amplitude of the N300 was shown attenuated in older adults, as reported in three studies

(West & Bowry, 2005; West & Covell, 2001; West et al., 2003). The age effect on the N300 seems to be attributable to the reduction in the efficiency of executive functions that would improve and support the detection of PM cues (West & Bowry, 2005). On the other hand, one study did not find an effect of age on amplitude of the N300 from adolescence to later adulthood (Zöllig et al., 2007). The failure to observe these age-related differences in the N300 amplitude has been suggested to be due to a differential recruitment of neural processes, earlier and later across lifespan, which may hide developmental changes in the amplitude of N300 when measures of average voltage are adopted.

The frontal positivity (or FN400) reflects a positivity that is greater for PM cues than for ongoing trials. It occurs between 300 and 500 ms after stimulus onset over the midline frontal sites of the scalp (West, 2007, 2011). Likewise to the N300, the frontal positivity is higher for PM hits than for both PM misses and ongoing trials (West, 2007). This frontal positivity has been linked to retrieval processes or to the process of switching between ongoing and PM task (Bisiacchi et al., 2009; West, 2011; West & Krompinger, 2005). The amplitude of the frontal positivity was shown attenuated in older adults relative to younger adults (West et al., 2003), suggesting age-related deficits upon these processes.

The parietal positivity was reported over the parietal sites of the scalp roughly at 400 ms when a PM cue is encountered, relative to ongoing trials (West et al., 2001). This sustained positivity is the result of three distinct and separate components: the P3b, the recognition old-new effect, and the prospective positivity (West, 2011; West & Wymbs, 2004). The contribution of the P3b on the parietal positivity might be minimized by adopting PM cues that are similar to the ongoing trials in terms of perceptual features (West, Wymbs, Jakubek, & Herndon, 2003). In contrast, the recognition old-new effect was shown to be related to the retrieval of the intention from memory, therefore it represents the retrospective component of PM (West & Krompinger, 2005). Finally, the third component, the prospective positivity (West & Krompinger, 2005) occurs later respect than the P3b and the recognition old-new effect, (West, 2007; West, Wymbs et al., 2003) and is associated with the configuration of the PM task, as well as, the coordination between PM and ongoing tasks (Bisiacchi et al., 2009; West, 2011). The parietal positivity is reduced in older adults than in younger later (West & Bowry, 2005; West & Covell, 2001; Zöllig et al., 2007). Studies that have explored which, among the three components, are the most sensitive to aging, revealed that a decrease in the amplitude of the P3b (West & Covell, 2001), and the prospective positivity (West & Bowry, 2005) contributed to the age-related

reduction in the amplitude of the parietal positivity.

In conclusion, age seems to affect all the ERPs associated with the realization of PM intentions, at least with respect to event-based tasks. The fact that there are no studies of this category of the ERPs on time-based tasks is easily understandable, given that time-based intentions are not linked to external PM cues.

2.3.2 Age effects on ERPs associated with strategic monitoring

Likewise to the studies exploring the ERPs elicited by PM cues, all the studies that have investigated the ERP correlates of strategic monitoring, focused uniquely on event-based task (Chen et al., 2007, 2009; Knight et al., 2010; West et al., 2006, 2007; West, 2007; West, Scolaro, & Bailey, 2011). Significant modulations were found in the ERPs elicited by ongoing trials, in which the occurrence of the PM cue was monitored (Chen et al., 2007; Knight et al., 2010; West et al., 2007). Therefore, these ERP modulations were interpreted as reflecting the allocation of attention required for strategic monitoring of the presence of the PM cue (Knight et al., 2010; West et al., 2007). Specifically, West and collaborators highlighted a sustained activity expressed as an enhanced negativity over occipital-parietal regions coupled with a positivity over frontal regions, beginning at roughly 200-400 ms after stimulus onset (West et al., 2006; West and Bowry, 2005). Another study suggested that such a sustained frontal/occipital-parietal activity might be related to the target checking mechanism of Guynn's model (West et al., 2007; see Paragraph 2.1.3, for details on Guynn's model), however it did not allow to completely exclude the possibility that it also reflected the retrieval mode. Indeed, a later study considered this long-lasting activity, expressed over frontal and posterior regions, a likely candidate to be the ERP correlate of retrieval mode (West et al., 2011). Other works reported similar ERP modulations on ongoing trials, mainly expressed over the frontal regions (Chen et al., 2007; 2009), suggesting the recruitment of the frontal lobe for Strategic Monitoring.

A recent study (Knight et al, 2010) showed that strategic monitoring may influence also the earlier ERP components. Specifically, it revealed an enhanced early visual perceptual component at 140 ms post-stimulus over occipital-parietal regions. Furthermore, an enhanced occipital-parietal negativity and centro-frontal positivity were found reaching the maximum of amplitudes at 220 ms post-stimulus. The study supported the idea that the preparatory attention required for strategic monitoring may act by improving processing of

PM cue features.

A recent study explored commonalities and differences in the ERP modulations of strategic monitoring in event-based and time-based PM tasks (Cona et al., in press). Three types of modulations characterized the ongoing trials in PM block (during which PM task was added to the ongoing activity). A frontal/prefrontal sustained modulation was shown in both the two tasks (time-based versus event-based). This modulation, starting at 180 ms post-stimulus and lasting for several hundred milliseconds, seemed to reflect the memory mechanism of holding the prospective intention in mind, (i.e. the retrieval mode). This is the first evidence of the electrophysiological correlate of strategic monitoring mechanism in the time-based PM. In addition, two other modulations were specifically observed in event-based task. An early modulation (130-180 ms post-stimulus), broadly distributed over the scalp, could be the expression of the attentional allocation to the stimuli for being in a 'readiness mode' to detect the PM cue. A later modulation, expressed as an enhanced positivity over occipital and parietal regions at 400 ms post-stimulus, might reflect the increased recruitment of resources required for checking the occurrence of PM cue.

The effects of aging on the ERP correlates of strategic monitoring have been examined only with regard to event-based PM task (Mattli et al. 2011; West & Bowry, 2005). Moreover only two studies have investigated this issue leading to contrasting results (Mattli et al. 2011; West & Bowry, 2005). Both the studies reported that slow wave modulations related to strategic monitoring were observed in younger and older adults. West and Bowry (2005) reported some age-related differences in the temporal dynamic and scalp distribution of these modulations. As revealed by scalp salience obtained by Partial Least Squares (PLS) analysis, younger adults showed long-lasting modulations over frontopolar and parietal sites, whereas older adults displayed sustained modulations only over central sites. On the other hand, Mattli and collaborators (2011) failed to find different modulations between older and younger adults.

There are no studies that have explored the effects of aging on the ERP correlates of strategic monitoring in the context of time-based tasks. Therefore, we conducted a study that investigated the age-related differences in the ERPs elicited by ongoing trials when a time-based PM task needed to be concurrently performed (Paragraph 2.4).

2.4 EXPERIMENT 1: ERP MECHANISMS UNDERLYING AGE-RELATED ALTERATIONS IN TIME-BASED PROSPECTIVE MEMORY

2.4.1 Introduction

The first chapter outlined how older adults show changes in a multitude of cognitive domains, especially in those functions that rely upon executive-control aspect of goals maintenance (Braver & West, 2008; Raz, 2000; West, 1996).

As several theorists have noticed, PM involves many components (e.g., planning an intended action, retrieving and executing the action) and particularly requires the intentions to be maintained active in mind (Dobbs & Reeves, 1996). Since alterations of information maintenance are hypothesized to characterize cognitive aging, they would have a role also in determining age-related decline in PM (Braver & West, 2008). Only a handful of studies have directly investigated the neural mechanisms underlying age-related changes in PM (Mattli, Zöllig, & West 2011; West & Bowry, 2005).

Therefore, the present study used event-related brain potentials (ERPs) to explore the effect of aging on the neural correlates the time-based PM. To our knowledge, no neuroimaging or electrophysiological study has ever explored the ERP bases reflecting age-related decline in time-based PM performance.

In general, PM tasks have been classed into two main categories: event-based and time-based tasks (Einstein & McDaniel, 1996). In event-based PM tasks, individuals execute an action in response to a certain event (e.g., posting a letter when a post box is seen) whereas in time-based tasks individuals carry out the intended action at a particular time or after a time interval (e.g., taking medication at noon or every twelve hours). In both the two kinds of task, the intended actions are accomplished while performing other ongoing activities and are retrieved without an explicit prompt from the environment.

Several models have been proposed to describe processes composing PM (see Paragraph 2.1.3) but the majority of these models focused on event-based PM (e.g., Burgess & Shallice, 1997; Guynn, 2003; McDaniel & Einstein, 2000; Smith & Bayen, 2004).

Among these, Guynn's model (2003; 2008) was developed in the context of event-based PM and then theoretically extended to the time-based one. This model is centred on the

role of strategic monitoring processes required for the realization of the intentions (Guynn, 2008). Specifically, Guynn postulated that accomplishing future intentions is mediated by two different components of strategic monitoring: the retrieval mode and target checking. Retrieval mode is conceptualized as a neurocognitive set, continuously required for maintaining the intentions activated in memory. It is also thought of as a 'task set', hence a cost on the ongoing activity (i.e., the PM interference effect) is predicted when individuals instantiate a retrieval mode or switch between retrieval modes (e.g., the retrieval modes of the PM and the ongoing tasks). On the other side, target checking is a more intermittent mechanism, and consists of checking the environment for the appropriate occasion to execute the intended action. In time-based tasks, target checking is carried out by monitoring the passage of time (e.g., checking a clock).

A more dated model, called the Test-Wait-Test-Exit (TWTE) model, well described how individuals usually manage time monitoring during a PM task (Harris & Wilkins, 1982). According to this model, individuals encode the PM instruction, and then wait for a certain period of time until a test of the time (checking the clock) seems appropriate. If the appropriate time has not elapsed, they wait until another clock check seems appropriate. The exit of this loop happens when the critical time occurs and the intention is executed.

The importance of time monitoring (i.e., the target checking component in Guynn's model) is corroborated by the fact that individuals tend to increase their clock checks when the critical time is approaching, as consistently revealed by several studies (Mäntyla & Carelli, 2006, for an overview).

Concerning the age effect on PM, there is a general agreement, across laboratory studies on PM, towards a deleterious effect of age on time-based PM performance (Bastin & Meulemans, 2002; Henry, MacLeod, Phillips, & Crawford, 2004; Jäger & Kliegel, 2008; Park, Hertzog, Kidder, Morrell, & Mayhorn, 1997; Uttl, 2008). One of the factors determining age-related differences in time-based performance seems to be the high recruitment of self-initiated retrieval and monitoring processes (e.g., Craik, 1986; d'Ydewalle, Bouckaert, & Brunfaut, 2001; Einstein et al., 1995; Jäger & Kliegel, 2008; Mäntyla, Missier, & Nilsson, 2009; McFarland & Glisky, 2009).

Originally, Craik (1986) proposed that prospective remembering is particularly sensitive to aging, as compared to other kinds of memory, because it is characterized by a lower extent of environmental support (e.g., explicit reminders, external memory cues) and a higher extent of more self-initiated retrieval processes. Since aging affects the availability

of controlled and attentional resources required for these self-initiated retrieving and retaining processes, a greater effect of aging has been found in prospective than retrospective memory tasks (Cockburn & Smith, 1991; Mäntylä & Nilsson, 1997; Maylor, 1993, 1996; but see Henry et al., 2004; Uttl, 2011). According to Craik's (1986) framework, when the environment is supportive for the intention retrieval – that is, the PM task is low demanding or provides external memory cues – older adults can allocate sufficient resources to perform the task, or compensate their reduced amount of resources by using external aids. If these conditions are not satisfied, older adults show a decline in PM performance, as observed in a large number of studies (e.g., Bastin & Meulemans, 2002; Einstein et al., 1995; Henry et al., 2004; Jäger & Kliegel, 2008; Mäntyla et al., 2009; McFarland & Glisky, 2009; Uttl, 2008).

Mäntyla and collaborators (2009) investigated the effect of age on time-based PM performance by varying the resource demands of the concurrent ongoing task. They found that, when the ongoing task was low demanding, older adults showed a PM performance similar to that of younger adults. However, to obtain a similar level of performance, older adults checked the clock more frequently in respect to younger adults, and this monitoring strategy led to a cost on the ongoing task. On the other hand, when the ongoing task was high demanding, older adults reduced the frequency of clock checks, and consequently had a worse PM performance as compared to younger adults. In line with Craik's theory (1986), the authors proposed that older adults were able to use external aids (i.e., clock checks) as a compensatory strategy in low demanding conditions, given that not all the resources were absorbed by the ongoing task; whereas in the high demanding condition, they did not have sufficient resources to adopt the same compensatory strategy, so they checked the clock less frequently and had an impaired PM performance.

An alternative, although not opposite, account for the age-related deficits in PM tasks is the "theory of cognitive control" (but in this context preferably called "goal maintenance account", Braver & West, 2008). According to this view, older adults have difficulties in the representation and maintenance of goal information over some extended period. In the case of time-based PM tasks, difficulties in maintaining active the goal (i.e., the intention) would lead to failure in executing clock checks at the appropriate time and/or to correctly execute the intended action (McFarland & Glisky, 2009). Borrowing the classification of strategic monitoring mechanisms from Guynn's model (2008), older adults would have an impairment in the retrieval mode mechanism, since retrieval mode properly consists of

maintaining the intention active in mind.

Several findings support the goal maintenance account. First, older adults are reported to think less often about the PM intention than middle aged and younger adults, as shown by Maylor's study (1998). Second, age-related differences in PM tasks were particularly pronounced when individuals had to maintain intentions in mind for as little as five seconds, before realizing them (Einstein, et al., 2000; McDaniel, Einstein, Stout, & Morgan, 2003). Third, older adults tend to check the clock less frequently than do younger adults (Bastin & Meulemans, 2002; Einstein et al., 1995; Park, Hertzog, Kidder, Morrell & Mayhorn, 1997). Finally, the goal maintenance account postulated that the age-related impairment in the ability of maintaining the goal information is mediated by a decline in the prefrontal cortex (PFC; Braver & Barch, 2002; Braver & West, 2008), which has been shown to play a key role in PM (e.g., Bisiacchi, Cona, Schiff & Basso, 2011; Costa et al., 2011; Gilbert, Gollwitzer, Cohen, Burgess, & Oettingen, 2009; Reynolds, West, & Braver, 2009; Burgess, Gonen-Yaacovi & Volle, 2011, for a review).

An increasing number of studies took into account the inter-individual differences in frontal-mediated processes to explain age-related deficits in PM tasks (Bisiacchi, Tarantino, & Ciccola, 2007; Gonneaud et al., 2011; Martin, Kliegel, & McDaniel, 2003; McDaniel et al., 1999; McDaniel & Einstein, 2011; McFarland & Glisky, 2009). Interestingly, McFarland and Glisky (2009) provided, although indirectly, a link between decline in frontal functioning and age-related impairments in time-based PM. In their study, older adults were classified as high or low in frontal functioning based on their performance on a battery of neuropsychological tests, and then were assessed in time-based PM tasks. Older adults characterized by low frontal functioning, as measured by neuropsychological tests, showed a worse PM performance, and less frequent clock checks than older adults with high frontal functioning. Interestingly, as compared to those adults with low frontal functioning, both young and older adults with high frontal functioning tended to monitor the clock more frequently as the crucial time for the PM intention was approaching. This pattern of results suggested that the frontal regions might be particularly involved in strategic monitoring processes.

The idea of a prominent role of the PFC in time-based PM tasks for strategic monitoring is consistent with recent findings with clinical populations (Burgess et al., 2008; Kliegel, Jäger, Altgassen, Shum, 2008; Troyer & Murphy, 2007; Volle, Gonen-Yaacovi, Costello, Gilbert, & Burgess, 2011), as well as with results from an imaging (Okuda et al., 2007) and

an electrophysiological (Cona, Arcara, Tarantino, Bisiacchi, in press) study. Surprisingly, so far no neuroimaging evidence has been provided on age-related changes in brain activity during PM tasks. Only two studies investigated the age effect on electrophysiological correlates of strategic monitoring, but with regard to event-based PM tasks and showing mixed results (West & Bowry, 2005; Mattli et al., 2011; see below for details).

The majority of electrophysiological studies investigated the ERPs elicited by the occurrence of PM events (West, 2011; for a review), whereas only a few studies focused on the ERPs in ongoing trials, reflecting the neural correlates of strategic monitoring (Knight, Ethridge, Marsh, & Clementz, 2010; Chen, Huang, Ren, Chen, & Yue, 2007; Chen, Huang, Jackson, & Yang, 2009; West, McNerney, Travers, 2007; West & Bowry, 2005; West, Scolaro, & Bailey, 2011). Most of the latter kind of studies compared the electrical brain activity elicited by ongoing trials in two conditions: when individuals have to merely perform the ongoing task (i.e., baseline block) *versus* when they have to concurrently fulfil a PM task (Chen et al., 2007; 2009; Knight et al., 2010). Recently, Cona and collaborators (in press) showed that the addition of both a time-based and an event-based PM task to an ongoing activity leads to a similar sustained and positive modulation of the ERPs in the ongoing trials, starting roughly at 180 ms post-stimulus and lasting until 800 ms. Such common activity, broadly distributed over the scalp but particularly pronounced over prefrontal and frontal sites, was thought to reflect the retrieval mode mechanism of strategic monitoring (see also West et al., 2011, for the ERP correlates of the retrieval mode in event-based tasks).

The effect of aging on the ERP correlates of strategic monitoring has been examined only with regard to event-based PM (West & Bowry, 2005; Mattli et al., 2011). The two studies that have investigated this issue led to partially contrasting results (Mattli et al. 2011; West & Bowry, 2005). Indeed, both the studies reported that slow wave modulations related to strategic monitoring were observed in younger and older adults. West and Bowry (2005) showed age-related differences in the temporal dynamic and scalp distribution of these modulations. As revealed by scalp salience obtained by Partial Least Squares (PLS) analysis, younger adults showed sustained ERP modulations over frontopolar and parietal sites. In contrast, older adults displayed these sustained modulations mainly over central sites. The authors suggested that younger and older adults recruit different neural generators for adequately coping with the increased demands needed to support strategic

monitoring (West & Bowry, 2005). On the other hand, Mattli and collaborators (2011) found that these sustained ERP modulations were similarly expressed in terms of timing and scalp distribution between younger and older adults.

Since no study has ever investigated the age-related differences in the ERP correlates of strategic monitoring with respect to time-based PM, the present study was designed to address this issue. To this end, we explored the ERPs elicited by an ongoing task in older and younger adults comparing them in two conditions: a baseline block, where the ongoing task was performed alone, and a PM block, in which a time-based PM task was simultaneously performed during the ongoing activity. The baseline block was always administered first, and the PM instructions were given only after performing the baseline block in order to avoid any carryover effect of keeping the PM intention in mind in a successive baseline block (Chen et al., 2007; Knight et al., 2010). This choice was also driven by the fact that the effects of strategic monitoring have still been shown in blocks where PM intentions were no longer relevant (Marsh, Hicks, & Cook, 2006; West et al., 2007). Importantly, the carryover effects of intention maintenance might be particularly remarkable in older adults given that they were shown to have difficulties in deactivating the intention even if it was no more relevant for the task (Scullin, Bug, McDaniel, & Einstein, 2010).

We expected that if older adults had difficulties in performing the time-based task, this should be reflected in some alterations of the ERP modulations associated with the addition of the PM task on the ongoing activity. In particular, an age-related alteration of the retrieval mode (i.e., in the 'intention maintenance' as conceptualized in the framework of goal maintenance account, Braver & West, 2008), would determine changes in those sustained frontal and prefrontal ERP modulations that were shown to reflect strategic monitoring processes (e.g., Chen et al., 2007; Cona et al., in press; Knight et al., 2010; West et al., 2011; West & Bowry, 2005).

2.4.2 Methods

Ethics Statement

The study was approved by the ethical committee of the Faculty of Psychology of the University of Padua and was conducted according to the principles expressed in the Declaration of Helsinki. All the participants were informed about the general procedure of the experiment and signed a written consent form.

Participants

Fifteen young adults and eighteen older adults took part in the study. Young adults were students recruited from the Faculty of Psychology at the University of Padua. They had a mean age of 23.81 years (SD = 2.01; range = 21-28 years; 10 females), normal or corrected-to-normal vision, and did not report previous neurological or psychiatric pathologies.

Older adults had a mean age of 67.77 years (SD = 5.41, range= 60-76 years; 12 females) and a mean education of 10.89 years (SD = 4.68), normal or corrected-to-normal vision, and no neurological or psychiatric pathologies. All older adults underwent a standard cognitive screening in order to exclude participants showing performance below normal ranges. The assessment included the Mini-Mental State Examination (MMSE; Folstein, Folstein, & McHugh, 1975) and a battery of Italian neuropsychological tests on working memory, divided attention, memory span, prose recall, and planning abilities (tests were taken from 'Esame Neuropsicologico Breve 2', tr. Short Neuropsychological Assessment 2; Mondini, Mapelli, Vestri, Arcara, & Bisiacchi, 2011). All participants were right handed, as measured by the Edinburgh Handedness Inventory (Oldfield, 1971).

Materials and procedure

Both the young and the older adults were administered the same experimental procedure, consisting of two blocks. In the first block, composed of 40 trials, participants were asked to perform merely the ongoing task (*baseline* block). In the second block, which included a total of 350 trials, participants were required to perform a PM task in addition to the ongoing task (*PM* block). Before the *baseline* block, ten practice trials were run to familiarize participants with the ongoing task.

Ongoing task

The ongoing task was adapted from the dual-task paradigm used by Bisiacchi and collaborators (2009), and consisted of white strings of five letters, pseudo-randomly presented at the centre of a black computer screen. The letters in the first, third and fifth positions were always identical, whereas the letters in the second and fourth positions could be the same or different. Participants were instructed to press a key on a response box with their right index finger if the letters in the second and fourth positions were the same (e.g. DFDFD) and another key with their right middle finger if they were different (e.g. DFDGD). All responses were given with the right hand, and response keys were counterbalanced across participants. Each trial began with a blank screen with a pseudorandom duration (ranging from 1700 to 2600 ms). The five-letter string was then displayed either for 1600 ms or until the participant response (maximum response time = 1600 ms). A second blank screen followed the string presentation. The duration of this second blank screen was determined online so that overall duration of stimulus presentation plus the second inter-trial interval was 3000 ms. No feedbacks on performance were provided.

PM task

In the PM block, in addition to the ongoing task participants were instructed to press a key on the left side of the response box with their left index finger, every 5 min from the beginning of the task, trying to be as accurate as possible. When the key was pressed, a digital clock appeared on the centre of the screen, showing the exact time in minutes and seconds. The digits had the same font and colour as the letters of the ongoing task. Participants were not informed about the duration of the PM block, which lasted about 27 minutes. This duration allowed the participants to perform up to five PM responses (i.e. at 5:00, 10:00, 15:00, 20:00, 25:00 min). To help them to estimate the passing of time, they had the opportunity to check the digital clock in any moment of the task by pressing another key (labelled with a clock icon on the response box) with their left middle finger. They were instructed to feel free to check the clock whenever they liked and as often as they needed. They were also instructed not to count the trials elapsed to estimate time. When they pressed the key to check time, the digital clock appeared in the centre of the screen.

Electrophysiological recording and data analysis

EEG was recorded (EEG equipment: System Plus, Micromed, Mogliano Veneto, Italy) from an array of 30 Ag/Ag Cl scalp electrodes mounted on an elastic cap (ElectroCap International, Inc.) and positioned according to the 10–20 International System [47]. The montage included the following scalp positions: Fp1, Fpz, Fp2, F7, F3, Fz, F4, F8, FC3, FCZ, FC4, T3, C3, Cz, C4, FT7, FT8, T3, T8, T5, CP3, CPZ, CP4, P3, PZ, P4, T6, TP7, TP8, O1, O2 and right mastoid. Eye movements were monitored by two electrodes, with one electrode placed above the right eye, and one placed on the external *canthi* of the left eye. The EOG (electrooculogram) was recorded with a bipolar montage. All electrodes were referenced to the left mastoid and re-referenced offline to the average of the left and right mastoids. The ground electrode was placed in AFZ. Data was recorded with a band-pass filter set at DC-50 Hz and digitized at a sampling rate of 512 Hz. Electrode impedance was kept below 5kΩ. Data processing was performed with EEGLAB 8.0.3.4b (Delorme & Makeig, 2004), running under Matlab environment (Version 7.4.0, MathWorks, Natick, MA, USA). Continuous EEG was resampled at 256 Hz and filtered between 0.1 Hz and 100 Hz. Then, it was segmented into epochs starting -3000 ms before the onset of the stimulus and ending 3000 ms post-stimulus. Epochs were locked to the presentation of ongoing stimuli (i.e., letter strings). Artefact correction was done on these epochs by using the Independent Component Analysis (ICA) toolbox in EEGLAB. ICA allows identification of independent signals (i.e., independent components) in the data. Among the independent components identified by ICA analysis, it is possible to distinguish which ones are mostly related to artifactual signals, such as blinks and ocular movements (Jung et al., 2000). The epochs containing clock checks or PM responses were excluded from the analyses. Epochs were digitally filtered with a low-pass 30 Hz filter. Afterwards, epochs were re-segmented, including 200 ms of pre-stimulus baseline and 1200 ms post-stimulus activity. Epoch rejection was performed with a threshold of ±100 μV. In the younger adult group an average of 1.33 % of epochs (SD = 1.85) were rejected in the baseline block, and an average of 7.25% of epochs (SD = 5.20) were rejected from the PM block. In the older adult group an average of 3.33 % of epochs (SD = 3.74%) were rejected in the baseline block and an average of 9.40 % of epochs (SD = 12.12%) were rejected from the PM block. Finally, only epochs with correct responses were analysed and averaged offline according to the block type (baseline and PM).

Behavioural data analysis

In order to evaluate the effect of aging on PM task, the accuracy of PM task was analyzed. A PM response was considered correct if the participant pressed the key for the PM response within ± 15 sec from the target time (e.g. for the 5.00 min response, a response within 4.45 and 5.15 min was considered as accurate). Performance on the PM response was analyzed by mean of a t-test with accuracy (codified as percentage of correct PM responses) as the dependent variable and Group as the between-participant factor (two levels: younger adults and older adults).

Performance on the ongoing task was investigated by means of two 2 × 2 mixed ANOVAs: one with mean response times (RTs) as the dependent variable and the other with mean accuracy as the dependent variable. The ANOVAs included the Group as the between-participant factor (two levels: younger adults and older adults), and Block as a within-participant factor (two levels: baseline and PM block).

Differences in the clock monitoring strategy were analyzed by means of a 2 × 5 × 5 mixed ANOVA. This ANOVA included one between-participant factor, i.e., Group (two levels: younger adults and older adults) and two within-participant factors: PM response order (five levels: from the first to the fifth PM response) and the five minutes preceding each PM response (five levels: from one to five minutes). Two within-participant factors were included to investigate respectively the changes in the frequency of time monitoring across the whole PM block and the changes in the frequency of time monitoring as approaching the time associated with each PM response (e.g., from the 1st to the 5th minute).

ERP data analysis

The ERPs elicited by ongoing stimuli (i.e. letter strings) were analyzed. Specifically, the ERPs of younger and older adults were compared between the Baseline and the PM block, in order to explore the ERP modulations due to the PM load. Differences in ERP modulations between the two groups were explored by comparing the mean amplitude of ERPs in different time windows. Driven by visual inspection, three early time windows were considered, i.e. 100-200 ms, 200-300 ms, and 300-400 ms. The sustained modulations of the late component (the P3) were analyzed in three time windows, i.e. 400-500 ms, 500-800 ms, and 800-1000 ms.

The analysis was conducted on the signal recorded on four electrodes over the midline

(Fpz, Fz, CPz, Pz), where the experimental effects were mainly expressed, according to a visual inspection of grand-averages. The laterality factor was not considered since visual inspection did not reveal pronounced differences between hemispheres. This result is in line with previous studies examining the ERP correlates of strategic monitoring, which showed none or negligible hemispheric asymmetries (Cona et al., in press, Chen et al., 2007, Chen et al., 2009, Knight et al., 2010).

Mean amplitudes were analyzed by means of separate mixed 2 × 2 × 4 ANOVAs, one for each time window. ANOVAs included a between-participant variable, Group (two levels: younger adults and older adults), and two within-participant variables: Block (two levels: baseline or PM) and Electrodes (four levels: Fpz, Fz, CPz, Pz).

In all ANOVAs, Mauchly's test was used to check sphericity assumption and Greenhouse–Geisser correction for sphericity departures was applied when required (Geisser & Greeinhouse, 1959). The effect size was quantified by means of η_p^2. Post-hoc analysis were performed to explore significant effects evidenced by ANOVAs by means of t-tests with p-values adjusted according to False Discovery Ratio (FDR) correction (Benjamini & Hochberg, 1995; Benjamini & Yekutieli, 2011). In the result section, only those post-hoc results relevant for the experimental design are discussed. Moreover, if interactions were significant, only post-hoc results referring to the interaction of the higher order are discussed.

All Statistical analyses were performed using R, release 2.13.1 (R development, core Team, 2011). ANOVAs were performed using the *ez* package (Lawrence, 2011).

2.4.3 Results

Behavioural results

Concerning the performance on PM task, the effect of Group on PM response accuracy was significant [$t(31) = 2.19$, $p < 0.05$], with younger adults (mean = 81%, SD = 25.60, range= 20-100%) showing an higher percentage of accuracy than older adults (mean = 55%, SD = 39.92, range= 0-100%). All participants were able to recall the PM instruction at the end of the experiment.

The analysis on the accuracy in the ongoing task showed no significant effects of Group [$F(1,31) = 0.24$, $p = 0.63$, $\eta_p^2 = 0.01$]), Block ($F(1,31) = 0.14$, $p = 0.71$, $\eta_p^2 < 0.001$], or the

Group × Block interaction [F(1,31) = 0.52, p = 0.48, $\eta_p^2 = 0.02$].

Concerning the analysis of ongoing RTs, as expected the ANOVA showed a significant main effect of Group [F(1,31) = 22.51, $p < 0.001$, $\eta_p^2 = 0.42$], with older adults having slower RTs than younger adults. The effects of Block as well as the Group × Block interaction were not significant (respectively, [F(1,31) = 0.24, $p = 0.63$, $\eta_p^2 = 0.01$] and [F(1,31) = 0.12, $p = 0.73$, $\eta_p^2 < 0.001$]).

Block	**Ongoing RTs (ms)**	**Ongoing Accuracy (%)**	**Accuracy on PM Task (%)**
YOUNGER ADULTS			
Baseline block	762.15 (128.47)	96.00 (5.07)	/
PM block	764.11 (110.27)	97.00 (1.69)	81(25.6)
OLDER ADULTS			
Baseline block	956.75 (129.82)	96.12 (3.83)	/
PM block	972.05 (155.19)	95.88 (3.89)	55 (39.9)

Table 2.1 Mean RTs and accuracy in ongoing and PM tasks.

However, a potential confound in RT analysis could be the practice effect generated by the fact that the PM block always followed the baseline block (this choice was necessary to avoid carryover effects, as explained in the Introduction). Specifically, an increase of RTs associated with the addition of a PM instruction to the ongoing task (the PM interference effect), could have been masked by the speeding-up of RTs because of a practice effect. A solution for partialling out the practice effect is to consider the Trial number as a covariate (i.e., each trial is associated with the ordinal number indicating its position within the whole experiment, i.e., the 1st trial, the 2nd trial, and so on, regardless of the block it belongs to). Similarly to a previous study (for details about the analysis, see supplementary methods of Cona et al., in press), we analyzed RTs including the Trial Number as covariate by means of Mixed effect regression (Pinheiro & Bates, 2000). As an additional value with respect to traditional regressions, Mixed effect regressions allow consideration of the

whole structure of data as a combination of fixed and random effects, leading to enhanced statistical power (Pinheiro & Bates, 2000, Baayen, Davidson, & Bates, 2008). The mixed model fitted on data had the following initial structure: one dependent variable, five variables included as fixed effects and three variables included as random effects. RTs (log-transformed to reduce data skewness) were included as dependent variable. The five fixed effects considered were: `Group` as a two level factor (`Group=younger`, `Group=older`), `Block` as a two level factor (`Block=baseline`, `Block=PM`), `Response` required as a two levels factor (`Response=same`, `Response=different`), the `Group × Block` interaction, and `Trial Number`, included as a covariate. The random effects considered in the model were the effect of `Participants`, the effect of `Block nested within participants`, and the `random slope of Trial Number adjusted for participants`. By considering these variables as random effects, some sources of variance of data were taken into account in the model, thus improving the statistical power of the analysis. Starting from an initial model, which included all the variables, a backfitting procedure was employed: non-significant variables were excluded from the model one at a time, starting with the variable with the lowest | t |. The final model yielded by this procedure is shown in Table 2.2. Fixed effect parameters are to be interpreted as effects of traditional regressions. Table 2.2 shows the following results: RTs were slower for older adults compared to younger adults, RTs were slower in the PM block than in the baseline block, and slower when the required response was "different" compared to when it was the "same". Finally, a significant practice effect was found since RTs were significantly faster as the trial ordinal position increased. Since the effect of `Group × Block` interaction was not significant, and thus dropped in the backfitting procedure, the two effects of `Group` and `Block` are additive. The significance of random effect parameters indicates that taking into account some sources of variance improves the goodness of fit of the model.

Fixed effect parameters	**β (SE)**	**t**	***p* value**
Intercept Group = younger *Block* =baseline *Response* = "different"	6.60 (0.034)	189.46	0.001
Group = older	0.23 (0.046)	5.08	0.001
Block = PM	0.039 (0.017)	2.31	0.018
Response = "same"	-0.052 (0.003)	-14.56	0.001
Trial Number	-0.0001 (0.00005)	-3.14	0.003
Random effect Parameters	**SD**		
Participants	0.12		
Block nested within participants	0.06		
Random slopes for Trial number adjusted for participants	0.00026		
Residuals	0.20		

Table 2.2 Fixed and random effects of mixed model analysis.
P values of fixed effects were calculated through Markov Chain Monte Carlo sampling, as implemented in the function *pvals.fnc* of *languageR* package (Baayen et al., 2008, Baayen, 2011). Significance of random effect parameters were assessed by means of Likelihood ratio tests.

To summarize, mixed effects regression confirmed the age related differences in RTs found with ANOVA but also highlighted a significant PM interference effect. When taking into account practice effect and achieving enough statistical power, RTs in PM block were significantly slower than RTs in baseline block, in both younger and older adults.

The analysis of monitoring frequency showed the only significant effect of the 'minute preceding a PM response' [$F(1,28) = 46.13$, $p < 0.001$, $\eta_p^2 = 0.62$]. Results from this analysis indicate that the frequency of clock checks increased as the PM response approached, irrespectively of whether the PM response was the first, second, third, fourth or fifth. Post-hoc analyses showed that the frequency of clock checks was higher within the 5th minute, as compared to all the other minutes (all *ps* < 0.01). Moreover, the frequency of clock checks was higher in the fourth minute compared to the first and the second (all *ps* < 0.01), showing the typical sawtooth-like distribution of clock checks. No differences between younger and older adults were observed in the frequency of clock checks (mean younger adults = 19.6 (SD = 12.27), mean older adults = 16.76 (SD = 13.77), or in the distribution of these clock checks across the experiment.

ERP results

Average ERPs showed a different morphology in younger and older adults (Figure 2.2 and Figure 2.3, respectively). In both baseline and PM block, younger adults displayed ERP waveforms characterized by an early biphasic deflection at the 100-300 ms time window. Afterwards, a later positivity occurred at 400 ms and lasted until roughly 800 ms. The ERPs in older adults showed waveforms characterized by a single early peak at the 100-200 ms time window. This early deflection was followed by a negative peak starting at 300 ms and ending at 400 ms (presumably a N2). After such negativity, a sustained positivity was shown beginning at 500 ms and lasting until roughly 1000 ms (presumably a P3). No between hemisphere-differences appeared in baseline or in PM block.

Concerning the effect of PM load on ERPs, an early and a later ERP modulation characterized the ERPs of both the two groups, which had more positive ERPs in PM with respect to the baseline block. Nevertheless these modulations were expressed at different time points and with a different scalp distribution in the two groups. A qualitative inspection of the 'difference waves' (PM block minus baseline block, Figure 2.4) revealed

differences between the two age groups in terms of amplitude (over Fpz and Fz) and time course (as can be seen mainly over CPz and Pz electrodes). More interestingly, a modulation of the amplitude of the later component was observed over prefrontal sites in younger adults (with the ERPs being more positive in the PM block than in the baseline block), but not in older adults.

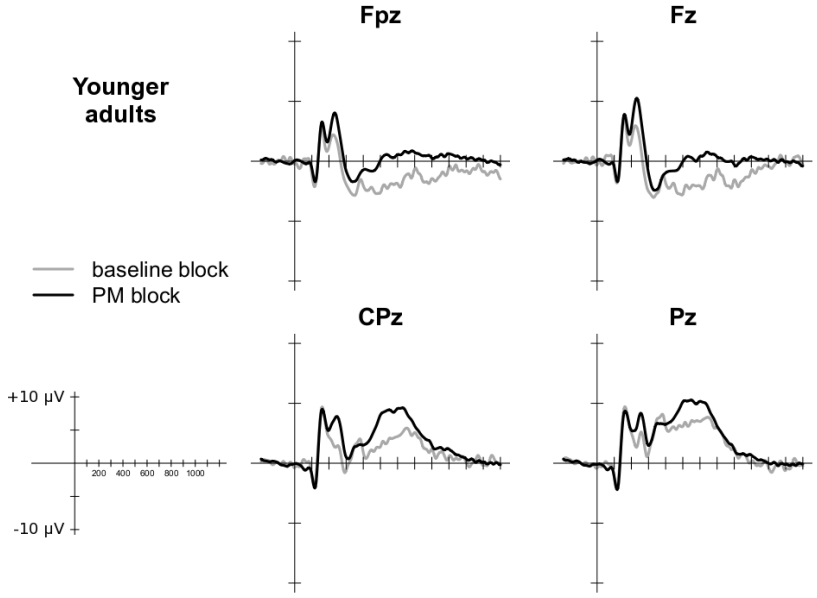

Figure 2.2 Grand average ERP waveforms in younger adults. The plots show the ERPs time-locked to ongoing trials in baseline block (gray line) and in PM block (black line) of the investigated electrodes.

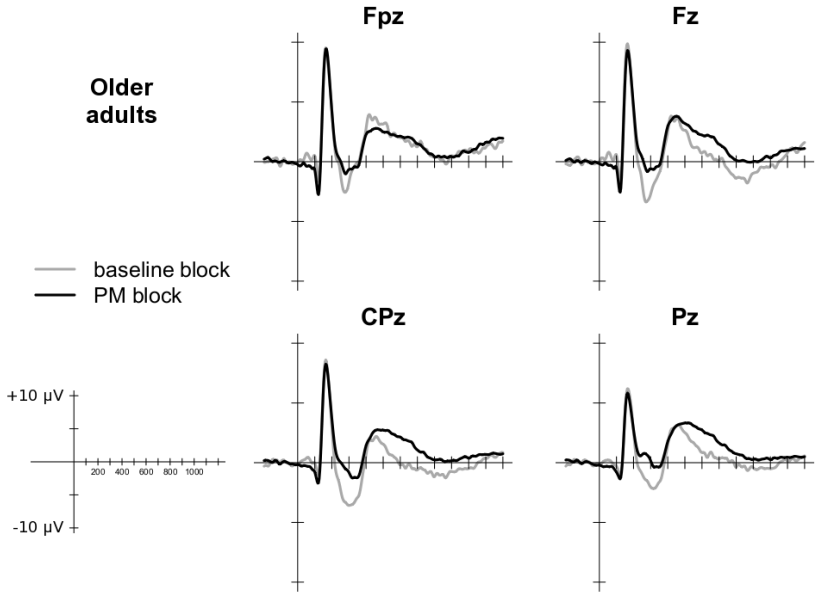

Figure 2.3 Grand average ERP waveforms in older adults. The plots show the ERPs time-locked to ongoing trials in baseline block (gray line) and in PM block (black line) of the investigated electrodes.

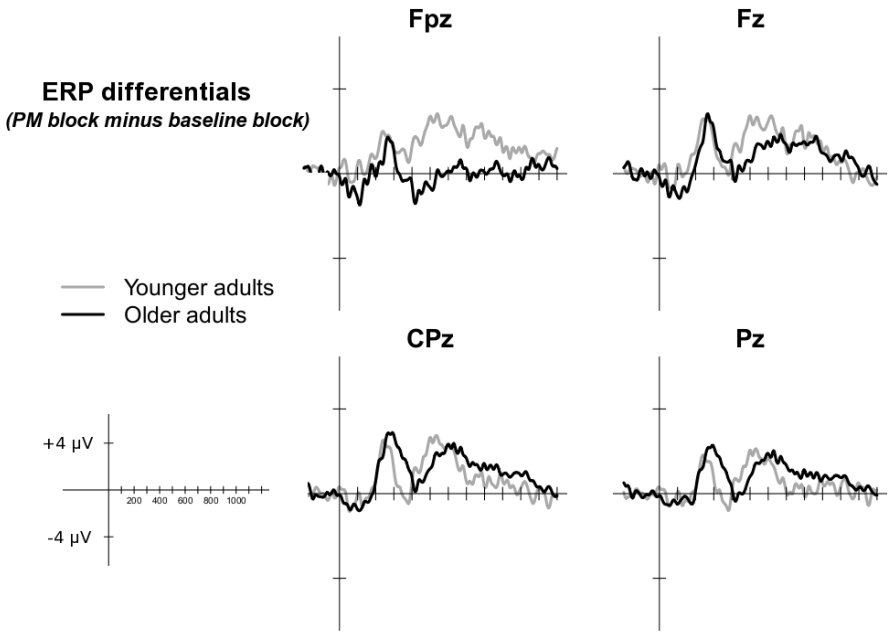

Figure 2.4 ERP differences in younger adults (gray line) and older adults (black line). The amplitudes shown are obtained as differences PM block-minus-baseline block of the ERPs time-locked to ongoing trials.

Early windows

100-200 ms

The first time window captured the first early peak of both younger and older adults. In this time window, the effect of Group was significant [$F(1,31) = 8.03$, $p < 0.001$, $\eta_p^2 = 0.21$] indicating that this early peak (P1) was higher in older adults than in younger adults. The significant Group × Electrode interaction [$F(3,93) = 10.17$, $p < 0.001$, $\eta_p^2 = 0.25$] indicated that in older adults the amplitude was lower in CPz than in all the other considered electrodes (all *ps* < 0.05).

200-300 ms

The second time window captured the second positive peak in younger adults and the descending arm of the early negativity (N2) in older adults. In this time window, only the effect of Block was significant [$F(1,31) = 25.79$, $p < 0.001$, $\eta_p^2 = 0.45$], indicating that, the

amplitude of the ERPs was higher in the PM block than in the baseline block, for both younger and older adults. This effect captured the modulations of the second positive peak - in younger adults - and of the descending arm of N2 in older adults. Although different waveforms characterized the ERPs between younger and older adults, however the ERP differential waveforms were similarly represented by a positive modulation due to the PM load, in the two groups (i.e. first peak of ERP differentials in Figure 2.4).

300-400 ms

The third window captured the ascending arm of the N2, in both groups. Three significant effects were found: the main effect of Electrode [$F(3,93) = 12.44$, $p < 0.001$, $\eta_p^2 = 0.29$], the Group × Electrode interaction [$F(3,93) = 34.81$, $p < 0.001$, $\eta_p^2 = 0.53$], and the Group × Block × Electrode interaction [$F(3,93) = 3.80$, $p < 0.05$, $\eta_p^2 = 0.11$]. Between-group post-hoc comparisons in the baseline block revealed that, as compared to younger adults, older adults showed more positive deflections over Fpz and Fz (all *ps* < 0.05), and more negative deflections over CPz and Pz (all *ps* < 0.05). A similar pattern was found in PM block, with older adults showing more positive deflections in Fz ($p < 0.05$), coupled with more negative deflections in Pz ($p < 0.05$) with respect to younger adults. Within-group post-hoc comparisons showed that older adults had a modulation of the ERPs in CPz, with the ERP deflections being more positive in the PM than in the baseline block ($p < 0.05$). In younger adults no significant differences between the PM block and the baseline block were found in this time window. In Figure 2.3 is observable how in older adults the N2 component over CPz is reduced (i.e., less negative) in the PM block as compared to the baseline block. Moreover, the fact that there is a significant difference in older adults, but not in younger adults, seems to indicate that the early modulation was more prolonged in older adults (as can be seen in the differential ERP waveforms, Figure 2.4). Indeed the early modulation started for both the younger and older adults at around 200 ms (hence in the previous analyzed time window). However, while in younger adults the effect ended around 300 ms, in older adults it was still evident in CPz at 400 ms.

Late windows

400-500 ms

The 400-500 ms time window captured the ascending arm of the late positive component, the P3. In this time window, the main effects of Group and Block were significant ([$F(1,31) = 8.22$, $p < 0.01$, $\eta_p^2 = 0.21$], [$F(1,31) = 4.63$, $p < 0.05$, $\eta_p^2 = 0.13$], respectively), as well as the main effect of Electrode [$F(3,93) = 12.73$, $p < 0.001$, $\eta_p^2 = 0.29$]. The Group × Electrode interaction [$F(3,93) = 25.21$, $p < 0.001$, $\eta_p^2 = 0.45$] was also significant. Post-hoc analyses revealed that the amplitude of ERPs was more positive in older than younger adults over Fpz and Fz (*ps* < 0.001), regardless of the type of Block. Furthermore, the interaction between Group and Block factors was significant [$F(1,31) = 4.70$, $p < 0.05$, $\eta_p^2 = 0.13$]. Post-hoc analyses indicated that only younger adults showed more positive ERPs in the PM block than in the baseline block ($p < 0.05$). The effect evidenced in this time window reflected the modulation, observed only in younger adults, of the ascending arm of the late positive component (P3). Indeed, as can be seen in both Figure 2.3 and in Figure 2.4, in this time window older adults did not show ERP differences between the PM block and the baseline block. This result seems to indicate that the later ERP modulation is delayed in older adults compared to in younger adults.

500-800 ms

The 500-800 time window captured the descending arm of P3. In this second late time window, the main effects of Block and Electrode were significant ([Block: $F(1,31) = 15.99$, $p < 0.001$, $\eta_p^2 = 0.34$; Electrode: $F(3,93) = 11.67$, $p < 0.001$, $\eta_p^2 = 0.27$, respectively,). Two interactions were also significant: the Group × Electrode interaction [$F(3,93) = 18.87$, $p < 0.001$, $\eta_p^2 = 0.38$], and the three-way Group × Block × Electrode interaction [$F(3,93) = 7.16$, $p < 0.01$, $\eta_p^2 = 0.19$]. Between-group post-hoc analyses of the higher order interaction showed that, in the baseline block, older adults had a more positive ERP deflections than younger adults in Fpz and Fz; whereas in CPz and Pz an opposite pattern was found, with younger adults having more positive ERPs compared to older adults (all *ps* < 0.05). Likewise, in the PM block older adults had more positive ERPs then younger adults (only in Fz), whereas younger adults had again more positive ERPs compared to older adults in both CPz and Pz (all *ps* < 0.05). More importantly, within-group post-hoc comparisons showed an ERP modulation, due to the PM load on the ongoing activity, that was different

between younger and older adults. Specifically, younger adults showed a more positive P3 in the PM block than in the baseline block, in all electrodes, but not Pz. Instead, older adults showed a more positive P3 in the PM block with respect to the baseline block, in all electrodes, but not Fpz (all *ps* < 0.05). In summary, post-hoc analysis of ERPs in this time window showed a positive ERP modulation related to PM load, in both younger and older adults. However, this modulation had a different topography in the two groups: more anterior in younger adults (the effect was present in Fpz, Fz, and CPz), and more posterior in older adults (the effect was present in Fz, CPz, and Pz). The differences in the ERP modulation over prefrontal regions between younger and older adults are clearly represented in the Figure 2.5, which displays scalp distribution of ERP differentials. Based on the results obtained by previous ERP studies (Cona et al., in press; West et al., 2011), the absence of a prefrontal ERP modulation in older adults seems to be a remarkable finding, and will be discussed below.

800-1000 ms

The last time window described the P3 modulation due to PM load, which appears to still be evident only in older adults. Three effects were significant: the main effect of Block [$F(1,31) = 9.75$, $p < 0.01$, $\eta_p^2 = 0.24$], the Group × Electrode interaction [$F(1,31) = 3.41$, $p < 0.05$, , $\eta_p^2 = 0.10$], and the Group × Block × Electrode interaction [$F(3,93) = 4.38$, $p < 0.05$, $\eta_p^2 = 0.12$]. The within-group post-hoc analyses of this interaction showed that only in older adults, ERPs were higher in the PM block than in the baseline block, in Fz, CPz and Pz (all *ps* < 0.05). In younger adults no significant differences between the PM block and the baseline block were found. As observable in Figure 2.2 and Figure 2.3, while a difference between ERPs in PM and baseline blocks was still shown by older adults, the same was not true for younger adults. Likewise to the previous time window (i.e., 500-800 ms), in this time window older adults also show an ERP modulation over all electrodes except Fpz (see scalp distribution of ERP differentials, Figure 2.4). In younger adults, instead, the positive modulation ended before, in the previous time window. This suggests that older adults had a more prolonged modulation of P3, due to the PM load, as compared to younger adults.

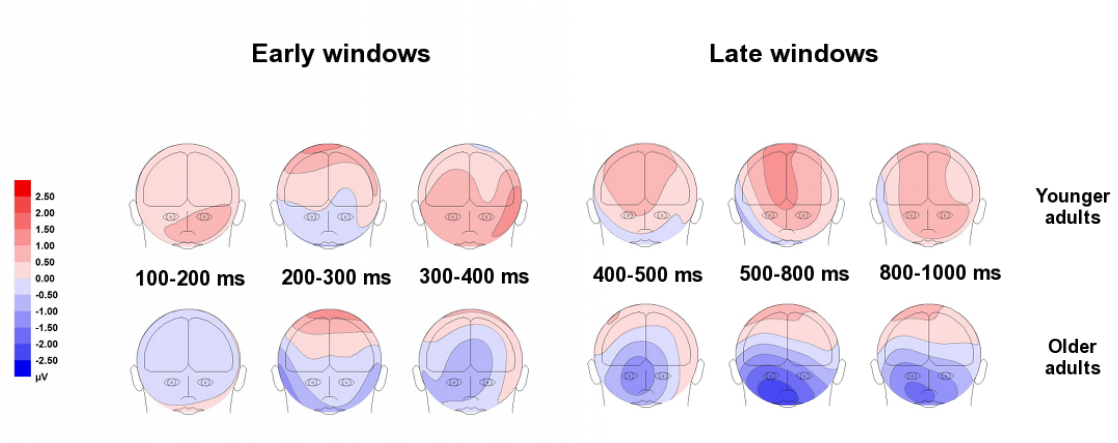

Figure 2.5 Scalp distribution of ERP differentials between baseline and PM block in younger and older adults (frontal view). The amplitudes shown are obtained as the mean amplitude in the PM block minus the mean amplitude in the baseline block. Average Maps are shown for the time windows in which the ERPs were statistically analysed.

2.4.4 Discussion

A large number of studies reported an age-related decline in time-based PM tasks (e.g, d'Ydewalle, Bouckaert, & Brunfaut, 2001; Einstein et al., 1995; Jäger & Kliegel, 2008; Mäntyla et al., 2009), nevertheless no study has ever investigated which neural or electrophysiological mechanism mediates such a cognitive decline. The present study was designed to explore the effect of aging on the ERP modulations associated with time-based PM processes, particularly focusing on those related to strategic monitoring. To this aim, the ongoing performance was specifically examined (Chen et al., 2007, Cona et al., in press; Knight et al., 2010; West et al., 2007; 2011).

In line with previous studies (Henry et al., 2004, and Uttl, 2008 for reviews), the present research showed a deleterious effect of age on the accuracy of time-based PM performance. The worse performance showed by older adults was accompanied by a similar number of clock checks between older and younger adults. These findings mirrors the pattern of results found in the high demanding ongoing condition in the study by Mäntyla and collaborators (Mäntyla et al., 2009). According to these authors, in the high demanding ongoing condition, older adults did not have sufficient attentional and controlled resources to adopt the same compensatory strategy used under the low demanding ongoing condition (i.e., the increased number of clock checks relative to young adults). The lack of sufficient resources led in turn to an impairment of PM performance.

This interpretation might be applicable also to our results. Indeed, although the ongoing task utilized in our study was not particularly demanding, it surely required more resources than did the ongoing task used for the low demanding condition in Mäntyla's study (i.e., listening to a short story). The idea that older adults had more difficulties carrying out the ongoing task (as compared to younger adults) was confirmed by the fact that they responded more slowly to this task already in the baseline block.

The effect of the addition of the PM task to the ongoing activity was expressed as a slowing in the ongoing RTs (i.e., the PM interference effect) in both younger and older adults, when partialling out the practice effect. The PM interference effect was not influenced by age, thus an equivalent slowing of RTs in the ongoing task, related to the PM addition, was found in the two groups.

The investigation of the ERPs elicited by ongoing trials when a PM task was added allowed us to better clarify the underlying mechanisms responsible for the age-related changes on PM as well as on ongoing performance. Specifically, the present study explored the effect of aging on the ERP modulations related to strategic monitoring (Cona et al., in press; West et al., 2011), which were evidenced as differences in the ERP amplitude between baseline and PM blocks.

Two ERP modulations associated with strategic monitoring were recognized in both younger and older adults' waveforms: an early phasic, and a later more sustained modulation. Both these ERP modulations were more prolonged and delayed in older compared to younger adults. In older adults the ERP modulations were expressed more extensively over parietal regions than over prefrontal regions as compared to the younger group. More specifically, in younger adults the addition of a PM task to the ongoing activity led to an early phasic ERP deflection in the 200-300 ms time window, expressed as an enhancement of a positive peak and widely distributed over the scalp. A later sustained modulation of the P3 occurred at 400 ms and lasted until 800 ms, expressed as an increased positivity over prefrontal, frontal and centroparietal sites. These two ERP modulations were different in the older adults in terms of time course and scalp distribution. The early ERP component was more prolonged, occurring in the time window between 200-400 ms, and it was mainly expressed over centroparietal regions as a decreased negativity (i.e., a less negative N2). After this modulation, a sustained increase of the P3 was found in older adults. As compared with the late sustained modulation showed by younger adults, such ERP modulation occurred later (at 500 ms), was more prolonged (roughly until 1000 ms),

and was expressed over frontal, centroparietal and parietal sites, but not over prefrontal sites.

A previous study (Cona et al., in press) interpreted such sustained frontal and prefrontal modulations as reflecting the process of maintaining the intention active in mind, that is the retrieval mode mechanism of strategic monitoring. Therefore, the absence of a prefrontal modulation in older adults might reflect an age-related impairment of the intention maintenance process (i.e., the retrieval mode) and gives support to the "goal maintenance account" (Braver & West, 2008). According to this theory, older adults would have difficulties in carrying out tasks in which goal information must be maintained over time, such as an intention as in the case of time-based PM tasks.

Even though West and Bowry (2005) explored the ERPs in an event-based PM task, they reported a similar pattern of findings, showing sustained ERP modulations over prefrontal regions in younger but not in older adults. This suggests that the absence of prefrontal modulation in older adults reflects the impairment of a strategic monitoring component shared by time-based and event-based tasks, which presumably is the retrieval mode. Finally, although the ERPs do not have a high spatial resolution, it seems likely that these ERP modulations reflect the PFC activity. This interpretation is also driven by several neuroimaging studies, which converged in revealing the crucial role of PFC in keeping the intention in mind (Burgess et al., 2011, for a review).

The comparison of ERPs in the baseline block between younger and older adults allowed us to better clarify a possible reason for the lack of prefrontal modulations in older adults.

Indeed in the baseline block, older adults showed a P3, which was more positive over prefrontal and frontal sites and less positive over centroparietal and parietal sites, as compared to the positivity displayed in younger adults. The finding that older adults generated a larger response at anterior sites than younger adults in a relatively easy task (i.e., the ongoing task in the baseline block) is consistent with previous electrophysiological studies (Daffner et al., 2001; 2006; Riis et al, 2008) and corroborates the 'posterior–anterior shift in aging (PASA) hypothesis' (Davis, Dennis, Daselaar, Fleck, & Cabeza, 2007; Rypma & D'Esposito, 1999; 2000). According to this view, older adults rely more heavily upon frontal processes to execute cognitive tasks. Specifically, this ERP response seems to be a neural compensatory mechanism that allows older individuals to carry out cognitive tasks at a level of accuracy comparable to their younger counterparts

(Cabeza, Anderson, Locantore, & McIntosh, 2002; Daffner et al., 2006), and is associated with the recruitment of more controlled resources even under rather easy conditions (Riis et al., 2008).

Since older adults recruited additional frontal and controlled resources to perform the ongoing task (as indexed by the posterior–anterior shift of P3), they would have no resources enough to adequately perform the PM task, leading in turn to an impaired PM performance. Therefore, it seems more reasonable that the impairment in the retrieval mode (i.e., in the intention maintenance), is not itself the primary cause of the age-related changes in PM tasks, but rather is in turn the consequence of the reduced amount of available controlled resources, as postulated by Craik's theory (1986). This would also account for the impaired PM performance and the absence of a compensatory enhancement of clock checks in older adults, conversely found in those studies with a low demanding ongoing task (Mäntyla et al., 2009; Maylor et al., 2002).

It is interesting to note that, when we considered the amplitude of the ERPs (as in baseline block), we observed a PASA pattern of the P3 (Daffner et al., 2006). On the other hand, when we considered the early and the late ERP modulations due to the PM addition (i.e., the ERP differential waveforms), we highlighted the opposite pattern of scalp distribution, with older adults having modulations that were more expressed over posterior regions as compared to younger adults. This pattern of results indicated that older adults recruited different neural generators respect than younger adults, as evidenced by West and Bowry' study (2005).

Taken together, the absence of prefrontal modulations coupled with the presence of parietal modulations observed in older adults, may extend the findings from those studies that have examined the effects of aging on working memory tasks (Cabeza, 2002; Cabeza et al., 2002; Daffner et al., 2011; Rypma & D'Esposito, 2000). Indeed, in order to carry out also time-based PM tasks, on one hand, older adults might presumably recruit the same neural generators (responsible for the prefrontal modulation) but less extensively than do younger adults; on the other hand, they recruit other neural generators (responsible for the parietal modulation), different respect those of younger counterparts. Differences between older and younger adults in the over- and under-recruitment of neural activity were thought to reflect age-related differences in the amount of available processing resources (The "compensation-related utilization of neural circuits hypothesis" (CRUNCH) model;

Reuter-Lorenz & Cappell, 2008; see Paragraph 1.2.6 of the present thesis for a description of this model).

Another noteworthy finding is the prolongation of the ERP modulations evidenced in older adults. A possibility is that the addition of the PM task to the ongoing activity could affect greatly the processing of ongoing stimuli in older compared to younger adults, although differences in RTs - in terms of PM interference effect - were not found between the two groups. This discrepancy between behavioural and ERP results confirms the importance of using alternative methods in order to study strategic monitoring, as claimed by Smith (2010). Furthermore, the more prolonged ERP modulations evidenced in older adults can be thought of as a slower return to baseline. Such phenomenon has been previously reported in other ERP studies in the literature of aging and has been interpreted as reflecting a more effortful and continuous processing of the stimuli (e.g., Fogelson, Shah, Bonnet-Brilhault, & Knight, 2010). Hence, in older adults, managing more tasks together, as the PM and ongoing task, seems to be more effortful, leading in turn to more prolonged and delayed ERP modulations. Since this is the first work that has investigated the effect of age on ERPs associated with time-based PM, it is difficult to ascertain the functional significance of these alterations. Therefore additional research is needed to explore age-related neural and electrophysiological changes related to specific time-based PM processes.

Summarizing, in this study we explored how aging affects the electrophysiological correlates of strategic monitoring in a time-based PM task. Firstly, an age-related difference on ERP modulations was found over prefrontal sites. The alteration of these prefrontal modulations in older adults seems to reflect difficulties in the intention maintenance (retrieval mode), which could be responsible for the impaired PM performance in older adults. However, impairment in the retrieval mode has been shown to be presumably the consequence of a reduced availability of controlled resources for carrying out the PM task (Craik, 1986), given that a large amount of frontal processing resources was allocated to perform the ongoing task adequately, as indexed by the PASA pattern of P3. Secondly, together with the absence of prefrontal ERP modulations, older adults displayed modulations that were more pronounced over parietal regions, as compared to younger counterparts. This pattern of results suggests that older and younger adults recruited different neural generators in order to support prospective memory. Moreover, it extends the findings observed in working memory tasks (e.g., Cabeza, 2002;

Reuter-Lorenz & Sylvester, 2005; Rypma & D'Esposito, 2000; 2001) indicating that aging is not simply associated with neural decline, but may also involve adaptive and compensatory neural responses.

CHAPTER 3

AGING AND EXECUTIVE CONTROL

3.1 AGING AND EXECUTIVE CONTROL: AN OVERVIEW

Chapter 1 of this thesis described how age-related differences concern a wide variety of cognitive tasks. It also dealt with the major theories that tried to identify the factors responsible for these changes.

Recently, attention has been drawn toward more process-specific accounts of cognitive aging, particularly focusing on executive control. Specifically, a group of theories, which will be clustered under the name of "Theory of Cognitive control", posits that age-related decline in executive control plays a crucial role in determining deficits in the other cognitive domains (Braver & West, 2008; Raz, 2000; West, 1996). According to this theory, one of the mechanisms underlying age-related cognitive changes is the deficit in the ability to represent and maintain goal information (see Chapter 1 for details). Decline of goal maintenance function has been found to account for a wide range of findings related to older adult performance (Braver et al., 2001; Braver & Barch 2002; Braver et al. 2005; Braver & West, 2008). Indeed, the process of maintaining task-goal representations is particularly important in several cognitive situations, such as when a strong competition between different responses occurs, or when response inhibition is required (Paxton et al., 2008). Moreover, deficits in goal maintenance among older adults were shown to be associated with age-specific changes in the prefrontal cortex (Braver &West, 2008; Paxton et al., 2008; Raz, 2000; West, 1996).

As more studies focused on executive-control processes, it has become increasingly evident that ‘‘executive control’’ is not a unitary construct, but seems to be composed of distinct types of processes (e.g., Friedman & Miyake, 2004; Miyake, Friedman, Emerson, Witzki, & Howerter, 2000, for an empirically derived classification of control processes; Sylvester et al., 2003). Specifically, Miyake and collaborators (2000) showed that

executive control could be subdivided into three separate types of processes: *updating*, *shifting* and *inhibition*. *Updating* consists of the evaluation of information and the revision of the existing contents in working memory as necessary by incorporating more recent relevant information and deleting the no longer relevant ones. *Shifting* (or switching) is concerned with the ability to shift attention between different tasks or different items of the same task. *Inhibition* is concerned with the ability to withhold dominant, automatic or prepotent responses when are inappropriate to the goals of the task. Although these three processes share some common elements, they are separable, with different executive tasks implying heavily just one or two specific processes. For example, performance on Wisconsin Card Sorting Test (WCST) was reported to be mediated primarily by shifting, the Tower of Hanoi problem by inhibition, and complex memory span tasks by updating.

A successive study (Fisk & Sharp, 2004) tested the Miyake and collaborators 's factor structure, including also older people. The authors confirmed the Miyake's model, and observed age-related deficits on all of those factors that were believed to correspond to updating, inhibition and shifting processes. Nonetheless, except for shifting tasks, which showed a less degree attenuation, such age effects were reduced to below statistical significance after controlling for age-related differences in information processing speed.

In line with this finding, a recent review of meta-analyses (Verhaeghen, 2011) highlighted that, in general, executive control has a modest role as explanatory mechanism for age-related changes in cognition when taking into account also the speed of processing factor. Moreover he found that some processes of executive control (for example inhibitory components such as the resistance to interference) do not show specific age-related deficits, whereas other ones (such as global task shifting, or switching, see below Paragraph 3.3.2 for details on global shifting) do show specific age-related deficits. Unfortunately, since too few researches exist to warrant a meta-analysis on updating, this process remained under-researched in Verhaeghen' study (for the same reason researches on age-related deficits in updating process will be only mentioned in this chapter).

The present chapter will provide an insight on age-related cognitive deficits in the three subcomponents of executive control, particularly focusing on inhibition and shifting. The updating process will be discussed in parallel with a specific kind of shifting-related processes, the attentional shifting (or switching), since these two processes have been usually studied together (e.g., Verhaeghen & Basak, 2005).

Given that an extremely large number of studies have been published on this topic, with

a multitude of executive tasks, the aim of this chapter will be not to review the findings of age effect on each single executive task, but rather to give a overview picture of how these processes are affected by aging, with a particular interest on ERP mechanisms underlying these age-related deficits.

3.2 AGE-RELATED CHANGES IN INHIBITION

3.2.1 Inhibitory processes

Inhibition "can refer to suppressing a stimulus that pulls for a competing response so as to carry out a primary response, to suppressing distractors that might slow the primary response, or to suppressing internal stimuli that may interfere with the current operations of working memory" (Nigg, 2000, p. 222).

This sentence makes clear that inhibition is not a single process, but concerns a series of functions. Several classifications have been proposed to clarify the different aspects of inhibitory processes (Hasher & Zacks, 1988; Nigg, 2000), as well as the different tasks most useful to tap these processes (Friedman & Miyake, 2004; Kok, 1999; Nigg, 2001).

Originally, Hasher, Zacks, and May (1999) put forth a taxonomy of inhibitory processes that distinguishes among three inhibitory functions: access, deletion, and restraint. Over the past 20 years, Hasher's works have focused on exploring the nature of inhibitory functions and showed that such processes are engaged across a wide range of cognitive tasks and that decline across lifespan (e.g., Hasher et al., 1999; Zacks & Hasher, 1994).

The access function of inhibition is required to determine which information enters inside the focus of attention, and which one is removed. When this function operates efficiently, the irrelevant information is suppressed whereas only the information that is relevant for the goals of the tasks can reach the level of consciousness. A clear example of this process is the "inattentional blindness" effect, where unattended stimuli, although being in the centre of visual field, are completely not seen (Mack & Rock, 1998).

The delete function serves to remove information that is no more relevant from working memory space, in order to allow an adequate processing of goal-relevant representations. Deletion also acts by removing once relevant information that became irrelevant given that a change in context, goals, situational demands, or tasks occurred. Deletion is required, for example, in a conversation when an argument changes, or in a

cognitive task when one set of procedure/instructions/stimuli ends and another begins. Vulnerability to the effects of no-longer relevant representations has been shown to vary across individuals, and to correlate with individuals' span scores, reading ability and intelligence tests (e.g., Chiappe, Hasher, & Siegel 2000; Dempster, 1991; Kane & Engle, 2000). Moreover, an inefficient process of deletion might negatively affect performance on apparently not related process, such as memory. Indeed, if deletion is inefficient, then the memory representing a given moment will not consist only of relevant information but also of irrelevant information that remained active in memory. This in turn will result in retrieval failures (e.g., Anderson & Bower, 1973).

The restraint function consists in controlling strong, but inappropriate, responses. It is probably the most frequently studied inhibitory function, and has been investigated with a variety of tasks, such as Stroop tasks, stop-signal tasks, anti-saccade task (see below, for a more detailed description of the tasks).

Nigg (2000) proposed another classification of the inhibitory processes that partially overlaps with the taxonomy putted forth by Hasher's group (Hasher et al., 1999). Nigg's (2000) taxonomy was based on the claims of Harnishfeger (1995), who suggested that inhibitory processes could be classified according to three dimensions. One dimension is the intentionality of the processes. Unintentional inhibition is implied prior to conscious awareness, for example in tasks involving the resolution of meaning for ambiguous words. On the other hand, intentional inhibition is needed when a stimulus/information is interpreted as irrelevant and therefore is consciously suppressed, for example when suppressing memory intrusions. The second dimension distinguishes between behavioral versus cognitive inhibition. Behavioral inhibition operates by controlling dominant but not appropriate responses, whereas cognitive inhibition acts by suppressing mental processes, unwanted or irrelevant thoughts, such as inappropriate meanings of polysemous words. The third dimension reflects a distinction between inhibition and resistance to interference. Specifically, inhibition actively acts through the suppression of the WM contents, whereas resistance to interference resembles a gating mechanism that prevents distracting stimuli or irrelevant information from entering inside WM (Wilson & Kipp, 1998).

Based on the conjunctions and separations of these three dimensions, Nigg identified four types of inhibition:

(a) **interference control**, which is the suppression of interference due the competition

between stimuli or resources, might be conceptualized as "intentional cognitive resistance to interference" and reflects, at least in part, the access function of Hasher's taxonomy;

(b) **cognitive inhibition**, which consists of the suppression of irrelevant information from WM, is "intentional cognitive inhibition" and is like the deletion function;

(c) **behavioral inhibition**, which is the suppression of prepotent responses, and mimes the restrain function for Hasher's classification;

(d) **oculomotor inhibition**, which represents the suppression of reflexive saccades and is "intentional behavioral inhibition" according to Harnishfeger's criteria (1995).

These separated inhibitory functions can be considered in the light of the classical three different stages required for information processing (Friedman & Miyake, 2004): (a) interference control (or access) happens at the perceptual stage, (b) cognitive inhibition (or deletion) occurs at an intermediate stage after contents enter in the focus of attention of WM (Cowan, 1995), and (c) behavioural inhibition (or restraint) intervenes at the output stage of processing.

Although the different types of inhibitory processes correspond to different stages of information processing, such correspondence does not imply that these processes are necessarily mediated by distinct inhibitory abilities (Friedman & Miyake, 2004). Indeed all seem to require some degree of executive control, and depend on the anterior attentional network (Posner & Raichle, 1994). For most of the functions discussed, there is increasing evidence for a crucial involvement of the frontal lobes, as shown from neuroimaging studies, studies involving patients with frontal lesions, and studies of aging (see Rabbitt, Lowe, & Shilling, 2001, for a review). Therefore, at least one feature is shared among the various types of inhibitory functions, that is the involvement of frontal lobes in performing the inhibitory tasks (e.g., Chambers et al., 2009; but see Konishi et al., 1999; Rubia et al., 2001).

Different tasks have been used to assess each of the three inhibition functions, and will be reviewed below.

ACCESS. The most widely utilized task for investigating access function is the Eriksen flanker task (Eriksen & Eriksen, 1974). This task underlines the importance of being able to selectively focus the attention on a specific stimulus, or an aspect of that stimulus, when it is embedded by some distracters that compete for processing. Therefore, the access function is also called 'Resistance to Distractor Interference' in several studies. In one of the task's versions, participants are instructed to identify to a central letter flanked either by

the same letters (e.g., HHHHH; compatible) or letters mapped to the other competing response (e.g., HHSHH; incompatible). Performance on incompatible trials was shown to be slower and less accurate as compared with performance on compatible trials given that the influence of the distractor stimuli negatively influence processing of the central letter.

Other commonly used tasks are the "word naming task" (Kane, Hasher, Stoltzfus, Zacks, & Connelly, 1994) in which, for example, participants are required to name a green target word that is shown either alone or together with a red distractor word. Similarly, the "Shape matching task" requires participants to indicate whether a white shape matches a green shape that is displayed either alone or together with a red distractor shape.

DELETION. One of the inhibitory processes that entails the deletion is the Resistance to Proactive Interference (PI), as proposed by Friedman and Miyake (2004). Resistance to PI consists of the ability to prevent memory intrusions from information that became no longer relevant to the task. This construct is similar to the processes related to access, as the Resistance to Distractor Interference, since they both involve interference control. Nevertheless two characteristics conceptually distinguish them. Indeed for Resistance to PI, the interfering information is presented before the occurrence of the target information and was previously relevant to the task. On the other hand, for Resistance to Distractor Interference, the interfering information is presented simultaneously with the target information and is never relevant (Friedman & Miyake, 2004). The tasks commonly used to assess the Resistance to PI are as follow. The Brown–Peterson task (Kane & Engle, 2000) engages participants to learn and later recall successive lists (List 1, List 2, and so on) that consist of words from the same category (e.g., animals). Failures in Resistance to PI are represented by the fact that participants intrude target words belonging to previous lists. The Paired associates task (Rosen & Engle, 1998) requires that participants learn and later recall several lists of cue–target word pairs to a criterion. In the interfering condition, participants learn some lists of targets that are paired with the same cues. For example, the design for the control condition might be EF-CD-AB (with lists being never the same) and the interference condition AB-AC-AB. List 2 recalling performance should be worse in the interference than in control condition because the List 1 cue-target associations should interfere with the other. The cued recall (Tolan & Tehan, 1999) requires participants to view alternatively one (control condition) or two lists (interfere condition) of four words each. Participants must retrieve the word on the most recent list belonging to a given cued category and ignore previous lists.

RESTRAIN, or inhibition of prepotent responses, is the most straightforwardly function related to active suppression and executive control. Suppressing dominant, but inappropriate, responses is a primary function operated by the supervisory attentional system (SAS), which is Norman and Shallice's (1986) model of executive control. The most representative tasks of response inhibition are: *i*) the Antisaccade task (Hallett, 1978) in which a cue flashes on one side of the screen but participants need to suppress the reflexive saccade toward it and instead look in the opposite direction in order to identify the target; *ii*) the simple go-nogo task (e.g. Menon et al., 2001), in which participants respond pressing a key when a target letter appears (e.g., Z, Y, or W), and withhold the response when an infrequent non-target occurs (e.g., X); *iii*) the stop-signal task (Logan, 1994), in which participants must identify and press as quickly as a possible a key button when a target letter appears (e.g., the X). On a small proportion of trials they must withhold their responses when they hear an auditory signal (or a visual stimulus, such as a red box; Chambers et al., 2006). On Stop trials, the manipulation consists of the stop-signal delay (SSD), which is the time between the onset of the target letter and the onset of the stop signal. Indeed, as the SSD increases, the likelihood of correctly suppressing the response decreases. Inhibitory performance is measured by the stop-signal reaction time (SSRT) that is the subtraction between the SSD at which the individual inhibits on 50% of Stop trials from the individual's mean RTs on Go trials. In healthy populations, SSRT typically ranges between 150–200 ms. In such a way, participants would require that stop-signal is presented 150–200 ms prior to their RTs to effectively inhibit the response on 50% of Stop trials; *iv*) the Stroop Task (Stroop, 1935) has been claimed to evaluate response inhibition processes. In this paradigm, participants must name the ink in which color words and neutral words are printed, ignoring the prepotent tendency to read the words.

In general, the suggestion that response inhibition involves controlled and limited-capacity processes are driven by studies showing that performance in these tasks is affected by concurrent cognitive load (e.g., Mitchell, Macrae, & Gilchrist, 2002; Roberts, Hager, & Heron, 1994) and by aging (e.g., Butler, Zacks, & Henderson, 1999).

Moreover, converging evidence from neuropsychology, neuroimaging and transcranial magnetic stimulation (TMS) studies has established that the pars opercularis of the right inferior frontal gyrus (IFG) plays a crucial role for inhibiting a prepotent motor response. Similarly, medial prefrontal areas, such as the supplementary motor area (SMA) and preSMA, have been shown to be implicated in mediating inhibitory processes (for recent

reviews, Aron, 2007; Chamber et al., 2009; Dillon & Pizzagalli, 2007). Recent studies on brain connectivity suggested that the IFG and SMA/preSMA might coordinate inhibition through direct white-matter tracts, as well as via the sub-thalamic nucleus of the basal ganglia (Aron, Behrens, Smith, Frank, & Poldrack, 2007).

3.2.2 Inhibitory processes in aging

One of the major theories of cognitive aging proposed that an important cause of age changes evidenced in cognitive tasks is the decline in the efficiency of inhibitory processes (Hasher & Zacks, 1988; Hasher et al., 1999). In general, aging resulted in poorer performance in a variety of paradigms that rely upon inhibitory processing, including stop signal task (Kramer, Humphrey, Larish, Logan, & Strayer, 1994), Stroop task (Houx, Jolles, & Vreeling, 1993), and antisaccade task (Butler, Zacks, & Henderson, 1999). However, other studies reported no age-related differences on tasks dependent on inhibition, such as on inhibition of return (Connelly & Hasher, 1993), or negative priming, in which a previously to-be-ignored stimulus has to be responded to (e.g., Buchner & Mayr, 2004). Since there is a large family of inhibitory processes (e.g., Friedman & Miyake, 2004; Nigg, 2000; Hasher et al., 1999) it is reasonable that age affects with a different extent the inhibitory processes.

The first distinction that may explain the different age effects on the various inhibitory tasks is the automaticity of the inhibitory processes, or, in other words, the intentionality according to Nigg (2000) and Harnishfeger (1995)' classifications. Indeed, given that older adults are known to have more difficulties on executive as compared to automatic processes (Hasher & Zacks, 1979; Jennings & Jacoby, 1993; Salthouse, Toth, Hancock, & Woodard, 1997; Titov & Knight, 1997), then aging should affect executive inhibitory processes to a greater extent than automatic ones. Kramer and collaborators (Kramer et al., 1994) provided first evidence supporting this claim. Indeed older adults had more difficulty than younger counterparts in a response-stopping paradigm and in the Wisconsin Card Sorting Task (WCST) task, which both involve executive and intentional inhibitory processes. On the other hand, both groups produced equivalent effects in negative priming paradigm, inhibition of return and response compatibility, which are paradigms that do not involve executive mechanisms.

Two recent studies (Andrés, Guerrini, Phillips, & Perfect, 2008; Collette, Germain,

Hogge, & Van der Linden, 2009) corroborated such view. Indeed these researches combined inhibitory paradigms implying a different extent of executive control. Andrès and collaborators (2008) showed that age affected Stroop interference and stop signal responsiveness (characterized by a high demand of executive control/ intentionality) but not negative priming (which is low demanding in terms of executive control/intentionality). Likewise, Collette and collaborators (2009), using different paradigms that required inhibitory processes on WM, came to the same conclusion.

Another distinction across the inhibitory processes can be made according to Hasher's taxonomy (Hasher et al., 1990), in which three different inhibitory functions are identified: access, deletion, and restraint.

Older adults often show deficits in access control of distraction, which sometimes disrupt and at other times facilitate older adults' performance, based on the link between distractors and targets. For example, older adults were shown to be slower in reading aloud when distractors were inserted in unpredictable locations in text (e.g., Carlson, Hasher, Connelly, & Zacks, 1995). Similarly, in a task requiring whether two letter strings (e.g., XPFGN and XPFCN) were the same or different, older adults resulted slower in the decision speed when other letter strings were simultaneously present respect when no distracter letters occurred (Lustig, Hasher, & Tonev, 2006). On the other hand, for young adults, the presence of distracters did not affect the speed at which letter-string decisions were solved.

Studies using Flanker task, one of the most representative tasks assessing access function (see Paragraph 3.2.1), have provided mixed evidence with regard to age-related differences in performance (for a recent review: Guerreiro, Murphy & Van Gerven, 2010). Indeed some of these studies showed that older adults were disproportionately slowed by incongruent flankers (e.g., HHSHH; Cerella, 1985, Experiment 3; Maylor & Lavie, 1998, Experiment 1; Zeef, Sonke, Kok, Buiten, & Kenemans, 1996), whereas more recent studies reported equivalent flanker interference across age (e.g., Collette et al., 2009; Falkenstein, Hoormann, & Hohnsbein, 2001; Fernandez-Duque & Black, 2008). In order to explain these mixing results, several factors have been taken into account as potential moderators of age effect. The variables that seem to influence the absence or presence of age-related differences in Flanker tasks are the distance between flankers and target (Cerella, 1985; Zeef et al., 1996) and the level of perceptual load or contrast (Maylor & Lavie, 1998).

Another issue of debate is whether the age effect is due to a failure in inhibiting

distractors or, alternatively, in activating relevant information. A number of findings suggest that activation processes are largely spared with age. For example, performance of older and younger adults was not different on a series of tasks involving activation but little or no inhibition (e.g., most repetition and semantic priming tasks, or categorization decisions; Hasher et al., 1999). Moreover, recent neuroimaging studies support the idea of impaired inhibition, but preserved activation for older adults. Gazzaley, and collaborators (2005) asked participants to look at alternating pictures of scenes and faces under conditions in which they were required to either (a) remember one of the two categories (e.g., faces) and ignore the other (e.g., scenes) and vice versa, or (b) passively view scenes and faces. When participants had to remember scenes, both younger and older adults showed somewhat equivalent activations, relative to the passive-viewing condition, in the area mediating scene processing (the left parahippocampal/lingual gyrus). When contrasting the passive-viewing condition with the ignore condition, younger adults showed less activation of these areas during the ignore condition with respect to passive condition, whereas older adults exhibited activations that did not differ across the two conditions. Therefore, both the groups were able to increase activation to the stimuli (in this case, the scenes) when they were relevant, but older adults displayed deficits in preventing the scenes, when irrelevant, from gaining access to the processing level.

Concerning the deletion function of inhibitory processes, older adults have been often shown to be less efficient in deleting no longer relevant information from WM. Indeed, in those paradigms requiring to forget some information in order to obtain a better memory for the relevant one, older adults tend to report more irrelevant information than their younger counterparts, suggesting that they have impairments in down-regulating no-longer-relevant contents (e.g., May, Zacks, Hasher, & Multhaup, 1999).

Age-related differences in the deletion function might also explain the effect of aging in WM capacity. Indeed the classical age differences seen on WM span tasks seem to be the result of a reduced ability to delete no-longer-relevant contents rather than a reduction in mental work space per se (see also Bunting, 2006; Friedman & Miyake, 2004; Hedden & Park, 2003). In other words, age-related differences in span tasks may not reflect age differences in the capacity of the WM per se, but might reflect age-related changes in the ability to keep WM free of irrelevant information. This claim is also confirmed by a study that revealed that all of the age-related variance in standard WM scores was explained by measures of the ability in delete function (Hambrick, Helder, Hasher, Zacks, & Swensen,

2005).

The last, and most widely studied inhibitory function is the restrain, which is referred to the ability to suppress strong responses that are inappropriate for a given situation. The Stroop task (Stroop, 1935) is the best-known paradigm of a larger class of response conflicting tasks and has been used frequently in the aging literature to examine response inhibition. The classic finding of interference in naming the ink color of incongruent colored words (i.e., RED presented in green) relative to ink-naming when words are congruent (i.e. RED presented in red) or neutral (i.e., not a color word, but XXXX presented in red) has been found enhanced in older adults (Verhaeghen & De Meersman, 1998; West, 1999). Interestingly, a large number of studies have found that this interference effect increases in an exponential fashion from the sixth to eighth decades (Uttl & Graf, 1997; van Boxtel, ten Tusscher, Metsemakers, Willems, & Jolles, 2001). Nevertheless, a meta-analysis (Verhaegen & De Meersman, 1998) showed that the slowed information processing with age could account, as a single function, for age-related differences in interference conditions (as well as in baseline conditions) of the Stroop task. Other evidence contradicted the claim that age-related differences in Stroop task performance are due to general slowing. For example, ERP studies of Stroop tasks indicated an age-related attenuation of frontal modulations reflecting inhibition, but did not report that reduction in processing speed influenced inhibition (West & Alain, 2000; see Paragraph 3.2.3, for details). However, the mixed literature regarding the mechanisms underlying increased Stroop interference effects in older adults suggests that these effects might reflect a conjunction of different processes rather than a pure index of inhibitory control, as has been supported by several studies using mathematical or computational modeling approaches (Cohen, Dunbar, & McClelland, 1990; Lindsay & Jacoby, 1994; Melara & Algom, 2003; Spieler, Balota, & Faust, 1996).

The effect of aging on performance in stop-signal tasks has been examined in a relatively little number of studies (e.g., Bedard et al., 2002; Kramer et al., 1994). Although these generally showed age-related impairment, the age effect on probability of suppressing a response is still not clear. Several authors reported that the probability of stopping was reduced in older adults relative to younger counterparts (May & Hasher, 1998), whereas some studies did not find such age-related impairment in stopping process (Bedard et al., 2002; Kramer et al., 1994; Williams, Ponesse, Schachar, Logan, & Tanoch, 1999).

The antisaccade paradigms have been used to explore the effects of aging on the ability to inhibit ocular responses (Butler et al., 1999). The antisaccade tasks require to generating eye movements in the direction opposite to the cued location. Studies examining the age effect of aging on performance of the antisaccade tasks have reported several consistent findings (e.g., Butler et al., 1999; Klein, Fischer, Hartnegg, Heiss, & Roth, 2001; Nieuwenhuis, Ridderinkhof, de Jong, Kok, & van der Molen, 2000). Saccade errors occurred more frequently in older adults than in younger counterparts in the antisaccade condition, while a similar number of errors was shown by younger and older adults in the prosaccade condition, in which the prepotent eye movement toward the cue was the correct response. Saccade latencies were often slower for older than younger adults in both antisaccades and prosaccades, although this age-related difference seemed to be typically greater for correct antisaccades (Munoz, Broughton, Goldring, & Armstrong, 1998).

3.2.3 ERP correlates of age-related differences in inhibitory processes

The ERPs offer a highly accurate method for examining the temporal dynamics of neural mechanisms underlying cognitive functions, and seem particularly suitable especially when no overt responses are required, such as in 'nogo trials'. The majority of researches in inhibition literature focused on the effects of age on the ERPs associated with response inhibitory processes. Two main ERP components have been commonly linked to inhibition. The N2 is a negative deflection peaking approximately 200 ms after the onset of an inhibition-eliciting stimulus, reaching its maximum amplitude over frontal regions (Eimer, 1993; Kopp, Mattler, Goertz, & Rist, 1996; van Boxtel, van der Molen, Jennings, & Brunia, 2001). The P3 (called nogo-P3) is a positive deflection peaking approximately 300 ms post-stimulus with a central or fronto-central maximum (Kok, Ramautar, de Ruiter, Band, & Ridderinkhof, 2004; Ramautar, Kok, & Ridderinkhof, 2006). In a classical go/nogo task, nogo trials are typically characterized by an increase in the N2 (e.g., Kopp et al., 1996) and the nogo-P3 amplitudes (Pfefferbaum & Ford, 1988) as compared to go trials, suggesting their role in response inhibition. Nevertheless, more recently, the functional significance of the N2 has been putted in doubt, with some studies showing a role in the detection of conflict between opposite responses, rather than in proper inhibitory processes (Donkers & Van Boxtel, 2004). In contrast, the inhibition-related meaning of the nogo-P3 has been supported by several recent stop-signal studies showing that the P3

seemed to have a source in, or close to, the primary motor cortex, a region responsible for mediating stop-signal inhibition (Kok et al., 2004; Ramautar et al., 2004). This claim is corroborated by the fact that P3 amplitude was shown larger in individuals with faster responses, which require a greater inhibitory recruitment to stop fast responses, relative to individuals with slower responses (Dimoska, Johnstone, & Barry, 2006).

In general the ERP studies with go/nogo tasks have found mixed results concerning the age effect on N2 and P3 amplitude in nogo trials. Some of these studies showed a reduction in the amplitude of N2 and P3 in elderly adults (e.g., Beste, Willemssen, Saft, & Falkenstein, 2010), whereas other studies reported equivalent, or even greater amplitudes of these components (e.g., Falkenstein, Hoormann, & Hohnsbein, 2002; Vallesi, Stuss, McIntosh, & Picton, 2009). On the other hand, there is consistently evidence of delayed peak latencies for both the N2 and P3 components in older adults (Fallgatter, Mueller, & Strik 1999; Horvath, Czigler, Birkas, Winkler, & Gervai, 2009; Pfefferbaum & Ford, 1988). However, it has been proposed that this slowing may reflect a general age-related slowing-down of processes rather than a selective impairment of inhibitory processes (Falkenstein, et al., 2002). Vallesi and collaborators (2009) recently proposed that these effects of slowing might reflect the fact that older adults strategically used more time to process conflicting stimuli. Moroever, in the study by Vallesi, the nogo P3 in irrelevant nogo stimuli was found to be greater in older respect than in younger adults. This findings might seem to be in contrast with some of the previous studies, which reported a less pronounced nogo-P3 in elderly (Pfefferbaum & Ford, 1988). The increased nogo P3 for irrelevant stimuli was interpreted as reflecting the increased attentional capture by irrelevant stimuli in aging.

Only one study (Anguera & Gazzaley, 2011) has examined the age effect on the ERPs elicited by a stop-signal task, which was created difficult enough to provide approximately 50% successful inhibition (SI) trials and 50% failed inhibition (FI) trials. Older participants exhibited a qualitatively comparable N2/P3 complex as compared to previous ERP studies that employed a stop signal task in young adults (Kok et al., 2004; Ramautar et al., 2004; van Boxtel et al., 2001). Nevertheless, older adults showed similar N2 and P3 peak amplitudes in SI versus FI trials, while N2 and P3 peak latencies were delayed in FI respect than in SI trials. The equivalent N2 peak amplitudes across the two types of trials might be due to the fact that older adults interpreted SI and FI trials as requiring an equivalent degree of conflict. Moreover, there was a negative correlation between N2 and

P3 amplitudes during SI trials, indicating that older adults with a greater N2 had a correspondingly larger P3. Interestingly, this relationship seems to provide evidence that the pre-motor inhibitory processes reflected by N2, such as conflict detection, might influence the ability of older adults to successively inhibit an action.

Another ERP component, the Lateralized Readiness Potential (LRP), has been commonly studied in the inhibition studies, although is not a specific index of motor inhibition. LRP reflects response preparation and is derived from the ERPs recorded over motor cortical regions that mediate right and left hand movements, and represents the net increase of negativity over the motor cortex contralateral to a prepared movement (De Jong et al., 1988; Gratton et al., 1988). For this reason, it is sensitive to partial unilateral response preparation (Eimer & Schlaghecken, 1998). Several studies have shown an abnormal activation (indexed by increased LRP amplitude) of the wrong response in older adults during conflicting conditions (e.g., Wild-Wall, Falkenstein, & Hohnsbein, 2008) as well as in nogo trials (Vallesi & Stuss, 2010), hence indicating age-related decline in inhibiting inappropriate responses.

Stroop tasks were largely used to examine the electrophysiological markers of age-related changes in inhibitory processes (e.g., Liotti, Woldorff, Perez, & Mayberg, 2000; West & Alain, 2000; West, Jakubek, Wymbs, Perry, & Moore, 2005). Specifically two neural correlates of conflict-response control are usually considered: the N450 and sustained potential (SP; Liotti, et al., 2000). The N450 is a phasic modulation occurring over the central regions between 400-500 ms after stimulus onset and reflects a greater negativity for incongruent stimuli (e.g., the word RED inked in green) than for congruent stimuli (e.g., the word RED inked in red; Liotti et al., 2000; West & Alain, 2000). The SP reflects a sustained parietal modulation between 500 and 800 ms after stimulus onset that represents an enhanced positivity for incongruent than for congruent stimuli (Liotti et al., 2000). While the N450 has been related to conflict detection, the SP has been associated with response selection (West et al., 2005). The amplitude of both the N450 and the SP was resulted attenuated in older adults (West & Alain, 2000). Moreover an age-related frontal shift has been evidenced in the topography of the SP in older adults, leading to the suggestion that younger and older adults may recruit different neural generators to support conflict and resolution processing (West, 2004).

3.3 AGE-RELATED CHANGES IN SHIFTING AND UPDATING

3.3.1 Shifting processes

Another subcomponent of executive control concerns shifting back and forth between multiple operations, tasks, or mental sets (Monsell, 1996). It is also referred to as switching and can be distinguished between "task switching" and "attentional switching" (also labelled "focus switching'', Verhaeghen & Basak, 2005).

Task switching. In a classical task-switching paradigm, participants are pre-trained separately on two or more tasks composed of a set of stimuli. Each task may require different processes, for example, to classify different elements or properties of stimuli, or to recall different attributes of the stimulus. Then, those stimuli are presented on each of a series of trials and the participants perform one of the tasks. The task sometimes changes from one trial to the next, and sometimes does not. Thus, it is possible to analyse performance on and following trials when the task changes in order to examine the extra processing demands that are related to the need to reconfigure task-set (Monsell, 2003).

Five phenomena are often measured when examining task-switching, and are described below:

- **Global switch costs** are obtained when comparing performance between task-switching and single-task blocks (Mayr, 2001).
- **Mixing costs** provide a purer index of switching, since the comparison between task-switching and single-task blocks concerns only repetition trials uncontaminated from local switch or restart costs. Mixing costs seem to reflect the maintenance of two or more task sets, or rules, in memory (Monsell, 2003).
- **Local switch costs** refer to the fact that participants are slower and less accurately when switching than when repeating a trial, thus on a 'switch trial' than on a 'non-switch' or task-repeat trial.
- **Restart costs** (Allport & Wylie, 2000) can be observed comparing the first response following a task-switch trial as compared with a task-repeat trial (Monsell, 2003). Restart costs have been associated with task-set (or, goal) activation, cue-task retrieval (Altmann, 2002), as well as the inhibition of responses needed in previous trial or task (Allport & Wylie, 2000).

- **Residuals costs**. If advance knowledge is provided of the upcoming task and time enough to prepare for it, the switch cost is usually reduced but not eliminated (therefore called 'residual cost').

Several paradigms are used to study task-switching processes. The alternating-runs paradigm (Rogers & Monsell, 1995) requires to alternate task every N trials, where N is predictable and constant, thus it is possible to compare task-repetition and task-switch trials within the same block. For example, an alternative paradigm consists in giving the participants short pre-specified sequences of trials (e.g. shape–color–shape), and to manipulate the available preparation time by changing the stimulus– response interval (Mayr & Keele, 2000). In contrast, in the task-cueing paradigm (Sudevan &Taylor, 1987), a cue appears in order to indicate which task, between two or more tasks, is required to be performed in each trial. In this paradigm, the time to change the task is unpredictable and the cue appears either before or with the stimulus. It is also possible to manipulate both the cue–stimulus interval (i.e., active preparation of task set) and the response–cue interval (passive dissipation of task set). Finally, in the intermittent-instruction paradigm, the sequence of trials is usually interrupted by an instruction that indicates which task has to be performed on the trial following that instruction. After the instruction, there is a 'restart cost' even when the instruction indicates continuing with the previous task, however is smaller as compared to when the task changes task (Allport & Wylie, 2000).

Attentional switching. The starting point for the description of attentional switching (or focus switching) is the embedded-process account of working memory, exemplified by the study of Nelson Cowan (1995, 2001). Cowan (1995, 2001) proposed a hierarchical two-tier structure for WM, characterized by a smaller zone of immediate access, called focus of attention (which contains the 'magical' number of 4±1 elements), from a larger zone of long-term memory required to hold information that is, although available, not immediately accessible (Figure 3.1). The recent extensions to Cowan's model by Garavan (1998), McElree (2001), and Oberauer (2002) highlight that the focus of attention is shown to be much narrower than previously hypothesized and it seems to hold no more than a single item at a given time. A relevant evidence for this narrow focus of attention comes from McElree's (2001) study with the *N*-Back task. In this task, participant is presented with a series of digits, one at a time, and has to press one of two possible keys to indicate

whether the digit presented on the computer screen is the same or not to the digit presented N positions back in the serie. McElree found that RTs were faster for N=1 than for either N=2 or N=3, but that RTs did not change between N=2 and N=3 (Figure 3.1). This indicates that only a single element at time can be held in the focus of attention. When N=1, the element must be retrieved from outside the focus of attention and moved into focal attention to be processed. This operation (i.e., attentional switching) determines a cost. The cost associated with attentional switching appears to be an all-or-none phenomenon – that is, the RTs increase is due to the presence of an attentional switch, regardless of the increases of the elements in WM. Otherwise RTs should have been slower from N=2 to N=3.

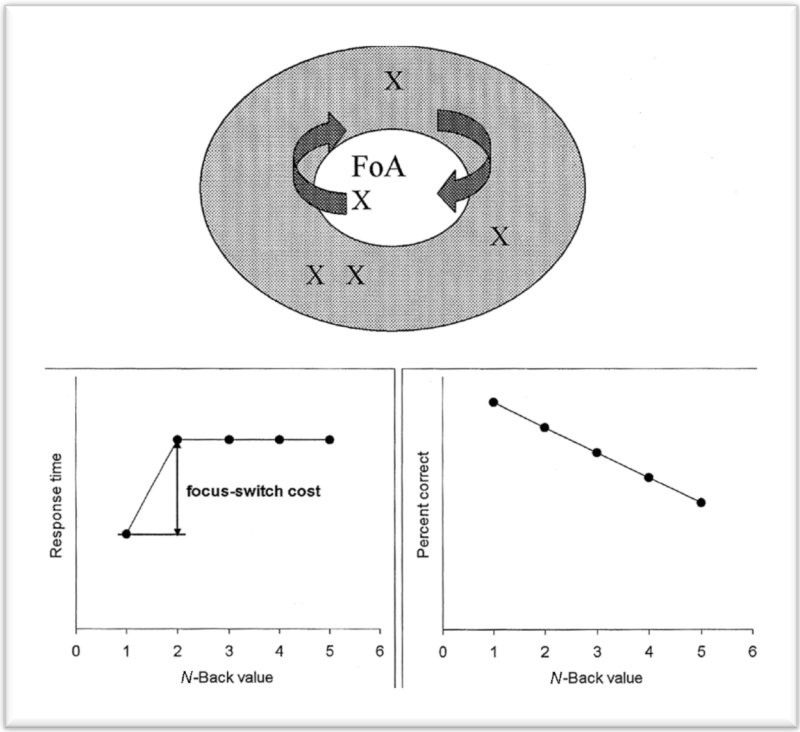

Figure 3.1 Model of attentional focus and expected results on attentional swiching. The top of the figure descibes the two-tier structure of working memory (McElree, 2001), with the focus of attention holding only a single element at a given time. The bottom of the figure shows the predictions for the identity judgement N-Back task based on this model: a step function in RTs (the size of the step defines the attentional switching effect) and a monotonic decline in accuracy as N value increases (adapted from Verhaeghen & Basak, 2005).

3.3.2 Updating *versus* attentional switching

Before describing updating in comparison with switching processes, it is important to provide a definition of WM updating. According to Morris and Jones (1990), updating consists in "modifying the current status of a representation of schema in memory to accommodate new input" (p. 112). This definition makes clear that updating implies not only the replacement of current memory elements by new contents, but also the modification of older elements according to newer information. In other words, the updating necessarily means that some aspects of the old information stay intact while other aspects change. Morris and Jones (1990) investigated updating using the running memory span paradigm (Pollack, Johnson, & Knaff, 1959). This paradigm requires participants to attend to a sequence of individual elements (e.g., consonants) and retain the N element most recent occurred, for subsequently retrieve them serially. Given that the onset of the recall cue is not predictable, participants need to continuously update their memory traces with the presentation of each new element. Another well-suited paradigm for studying updating processes is the N-back task, described in the previous paragraph. The n-back task is similar to the running span task, but with the additional requirement that participants must respond to each new element by judging it respect to the oldest element in the memory set (Owen, McMillan, Laird, & Ed Bullmore, 2005, for a review on N-back tasks).

In their work, Verhaeghen and Basak (2005) used a modified version of McElree's (2001) identity judgement N-Back task (see Paragraph 3.3.1) for studying not only attentional switching, but also updating-related processes. In their experiment participants, after having made the identity judgement, needed to replace in memory the item in the Nth position back with the item currently presented on the screen. However, this updating process was only required when the item presented in the Nth position back was different from the item currently presented (i.e., a "no" response); on the other hand no updating process was necessary when the items were identical (i.e., a "yes" response). The cost associated with updating was measured by comparing the RTs on "yes" and "no" responses. As expected, "no" responses, during which item updating was necessary, were 100 ms slower than "yes" responses for N=1, and 140 ms slower for the higher values of N. The increase of 40 ms for N values greater than 1 as compared to N=1 indicates that the updating and attentional switching processes cannot be serially executed without additional costs. One possible account is that attentional switching and updating are mediated, at least

partially, by the same cognitive structures in order to be carried out. Another possible explanation is that the necessity to switch between processes (i.e., between updating and attentional switching) is itself an executive-control process that represents an additional phase of processing. Interestingly, in this study, the authors also dissociated the effect of aging on updating and switching components, as will be described in the following paragraph.

3.3.3 Shifting and updating processes in aging

In the task-switching paradigms used in the aging literature, the main measures employed are the switching costs, which represent the contrast in performance between conditions in which tasks need to be changed across successive trials and conditions in which task are invariant (Paragraph 3.3.1). One of the most intriguing findings is that older adults showed consistent and robust age-related increases in mixing costs but smaller, or even absent, age-related differences in local switching costs (Kray & Lindenberger, 2000; Verhaeghen, Cerella, Bopp, & Basak, 2005; Mayr , 2001; Verhaegen, 2011).

Specifically, Kray and Lindenberger (2000) investigated the age-related differences in global (which are similar to mixing costs) versus local switching costs. In their study, global switching costs were measured by comparing the RTs in single task set conditions (e.g., a sequence of only AAAAAA trials) with the RTs in dual task set conditions (e.g., a sequence of AABBAABB). Local switch costs were calculated by comparing RTs of switch trials with RTs of repeated trials within the AABBAABB condition. Older participants showed increased global switch costs, but no differences in local switch costs, as compared to their younger counterparts. This suggests that age is associated with difficulty in maintaining several mental sets in mind, rather than in the difficulty to specific operate the switch. The present result was also supported by a meta-analysis carried out by Verhaeghen and Cerella (2002), which found that, after taking into account generalized age-related slowing, older adults showed enhanced mixing costs but no effects in local switching costs.

The finding of the age effect on mixing costs is also in line with the theory of cognitive control (also called the “goal maintenance account”, Braver & West, 2008), according to which older adults should have difficulties in maintain more task goals active in mind. Nevertheless, the minimal age effect on local switch costs seems surprising from the

standpoint of theory of cognitive control. It is becoming clear that local switch costs represent a complex mixture of variables, of which only some may be associated with task-set representation. Particularly, recent studies showed that switch costs are influenced by cue and response repetitions (Logan & Bundesen, 2003; Meiran, 2000), target-evoked associations (Allport & Wylie, 2000), higher-order sequential effects (Brown, Reynolds, & Braver, 2006) and predictability of the switch (Van Asselen & Ridderinkhof, 2000). Indeed, there is some evidence that older adults are mainly impaired in task switching when the switch needs be made at unpredictable intervals than at predictable ones (Van Asselen & Ridderinkhof, 2000). Kray, Li and Lindenberger (2002) suggested that, when switching process is unpredictable, local switch costs are higher for older adults because multiple mental sets are not being actively maintained across the entire sequence of trials.

Regarding the age effect on switching-related processes and updating, the study by Verhaeghen and Basak (2005; see Paragraph 3.3.2, for detail) highlighted two age-related dissociations: attentional switching was impaired in terms of accuracy in older adults, but no age-related sensitivity was shown either for updating or for global switching. Therefore, attentional switching seems to be the most vulnerable process to the effect of aging. These dissociations might be interpreted as evidence for the independence among components belonging to "executive control" (Perfect & Maylor, 2000).

In a later study, Verhaeghen and Hoyer (2007) focused on the specific effect of aging on attentional switching using a different task called 'continuous calculation task'. This task consisted of a series of single-digit numbers, presented one at a time on a computer screen. Participants were instructed to execute a calculation on the first pair, write an answer, combine this answer with the following number to perform the next calculation, and so on. Two kinds of calculations ("rules") were used depending on the nature of the numbers (e.g., if they were differed by two, or by one). Attentional switching was manipulated by putting participants to execute calculations on a single series ("single" condition) or two series, each one occurring in a different column on the screen ("dual" condition, attentional switching). They found that the attentional-switching cost (as difference in terms of performance between single and dual condition) was larger for older adults than for younger adults in terms of accuracy (see also Vaughan, Basak, Hartman, & Verhaeghen, 2008). This result is in line with the findings obtained in the previous work, and was ascribed to the greater interference in the WM zone outside the focus of attention in older adults. However, opposite results were shown by Oberauer's studies (Oberauer, Wendland,

& Kliegl, 2003; Oberauer, 2005). These studies found that attentional switching costs (called by the author 'object-switch costs') were smaller, or even absent, in older adults as respect to younger adults.

The studies that have focused on the effect of aging on updating process were few and led to contrasting results (Verhaeghen, 2011). Some studies showed that updating is vulnerable to age, with older adults having a worse performance as compared to younger adults in running memory tasks (Van der Linden, Bredart, & Beerten, 1994) or in other kinds of memory updating tasks (De Beni & Palladino, 2004; Hartman, Dumas, & Nielsen, 2001; Salthouse, Atkinson, & Berish, 2003). Nevertheless, other studies highlighted that, once general slowing effects were taken into account, no age-related differences resulted significant in the updating process performance (e.g., Fisk & Sharp, 2004; Fristoe, Salthouse, & Woodward, 1997; Verhaeghen, & Basak, 2005).

Taken together, these studies suggest that aging is associated with difficulties in maintaining multiple items, or tasks, active in mind (indexed by mixing costs), as well as in switching the attention from one item to another (indexed by attentional switching). On the other hand, the proper execution of switching between tasks (indexed by local costs), as well as the updating process, seems to be more spared with age.

3.3.4 ERP correlates of age-related differences in shifting and updating processes

The ERPs have been explored in a number of studies to examine the time course of the processes underpinning task switching. Specifically, this technique has been used to explore neural correlates of both mixing costs - reflecting differences in uncontaminated trials between conditions where individuals perform a single task and conditions in which they switch between more tasks - and local switch costs - reflecting differences between trials where individuals have to switch from one task to another (see Paragraph 3.3.1) (e.g., Kieffaber & Hetrick, 2005; Travers & West, 2008). Mixing costs are consistently associated with an enhancement in the amplitude of P3a and P3b components for mixed trials than for pure trials over the frontal, central, and parietal regions of the scalp (Eppinger, Kray, Mecklinger, & John, 2007; Kieffaber & Hetrick, 2005; Kray, Eppinger, & Mecklinger, 2005; West, 2004). Local switching costs are expressed over the parietal sites of the scalp, as a greater positivity for switch trials than for repeated trials (e.g., Kieffaber & Hetrick, 2005; Rushworth, Passingham, & Nobre, 2002).

Over the frontal sites, the effect of task switching (i.e., differences between switch and repeated trials) on the ERPs varies among the studies. As an example, Rushworth and collaborators (2002) observed, in a task requiring shifting mental sets (i.e., the stimulus–response matching), an increased positivity over the midline frontal regions for switch trials relative to repeated trials, occurring between 300 and 500 ms after cue onset. A similar frontal positivity has been described in other studies and has been interpreted as a modulation of either the frontal P2 or the P3a based on the timing of the effects observed (Kieffaber & Hetrick, 2005). Nevertheless, other studies have failed to show an effect of task switching on the ERPs over the frontal regions of scalp in this time interval (Travers & West, 2008), or have reported a greater frontal negativity for switch trials than for repeated trials (Miniussi, Marzi, & Nobre, 2005; West, Bailey, & Langley, 2009).

It is noteworthy that, together with the ERP correlates of switching, also the components related to the updating process were usually examined in studies on switching (see also Adrover-roig, & Barceló, 2010; Friedman, Nessler, Johnson, Ritter, & Bersic, 2008). Indeed, according to the interpretations formulated by Barceló Perianez and Knight (2002), when a cue (that informs to switch the task, or the rule) is presented in a switch trial, it triggers the reallocation of attentional resources towards the new task or rule, as indexed by the P3a. Afterwards, the new task needs to be updated, as reflected by the P3b component, which is the classical measure of contextual updating (Kray et al., 2005 and West & Moore, 2005 for the interpretation of the P3b as reflecting task-set updating).

Several studies examined age-related differences in the ERPs elicited by task switching (e.g., Adrover-roig, & Barceló, 2010; Barceló et al., 2002; Hillman, Kramer, Belopolsky, & Smith, 2006; Friedman, et al., 2008; Kray, Eppinger, & Mecklinger, 2005; Themanson, Hillman, & Curtin, 2006; West & Moore, 2005). Specifically, the studies by Barceló and colleagues (Barceló, 2003; Barceló, Perianez, & Knight, 2002) used a modified version of the Wisconsin Card Sorting Test (i.e., MCST), a computerized test to measure the ability to shift between cognitive sets or strategies in response to a change in the environmental. In this experiment (Adrover-roig, & Barceló, 2010), participants were required to match a card with the key cards depending on one stimulus dimension only (i.e., either the shape or card of items in the card). For example, participants were instructed to start sorting cards by a dimension (e.g., color), and then to alternate between this dimension and another one (e.g., shape). An auditory cue informed participants whether to switch or repeat the previous dimension-linked rule. Afterwards, it was presented a display with four key cards

above one choice card (target stimulus). Participants used a 4-button panel to match the choice card with one of the four key cards presented above (see Figure 3.2 for a schematic description of trials). ERPs were analyzed locked both to the cue and the target.

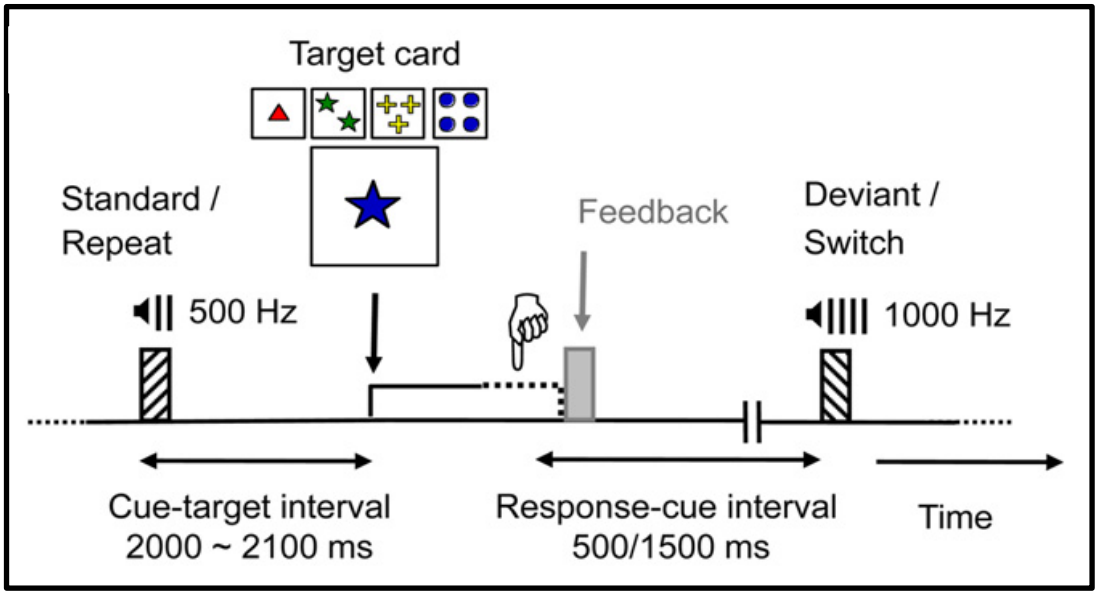

Figure 3.2 Schematic example of one MCST trial (adapted from Adrover-roig, & Barceló, 2010).

Switch trials (25%) were very infrequent as compared to the repeated trials (75%). In general, when a cue indicated that participants had to switch to a new dimension, a frontally P3a was elicited and was followed by a more posterior P3b component and a negative slow wave. Nevertheless, age did not affect the P3b elicited by the task-switch cues. This result suggests that the anticipatory updating of stimulus-response association in working memory, as indexed by such P3b, seems not to be impaired by aging. On the other hand, target-locked ERPs were greatly vulnerable to the effect of aging, with older adults exhibiting two well-known ERP patterns: (1) the compensatory ‘‘anterior shift’, or ‘PASA’ in target P3 for single-task condition, and (2) a decrease (as compared to younger adults) of fronto-central slow negativities in task-switching conditions.

Some of the studies that have examined the effect of age on P3b (Friedman et al., 2008; West & Moore, 2005) showed that this component was higher on switch respect to repeated trials in young adults, whereas was equivalent between switch and repeated trials in older adults. This pattern of results suggests that older adults need to update task sets even on trials that should not require an updating process. The lack of this differentiation in

P3b amplitude observed in older adults might has been attributable to an age-related deterioration of the fronto-parietal networks responsible for attentional control, as well as to an impairment of updating processes (Friedman et al., 2008; Milham et al., 2002).

A recent study (Daffner et al., 2011) used an N-back task, a classical paradigm of updating, to investigate the effect of age on scalp distribution of P3b. Younger and older participants executed a verbal N-back task with three levels of difficulty. Remarkable age-related differences were shown in the scalp distribution of the P3 component: older participant exhibited a higher P3 over anterior sites as respect to younger participants, reflecting the posterior–anterior shift in aging (PASA) pattern (Davis et al., 2008). This pattern seems to indicate that older individuals recruit more controlled frontal resources to face the task. Similarly, older participants exhibited a higher P3 over right hemisphere regions (usually less involved in verbal processes) than younger participants, whereas no age-related differences in terms of amplitude were observed over left hemisphere sites. These results are in line with the hemispheric asymmetry reduction in old age (HAROLD) model (Daselaar & Cabeza, 2005; see Chapter 1, for details on PASA and HAROLD patterns). This study underlined that aging is associated with the engagement of compensatory neural networks that would subserve the updating processes.

Concerning the ERP correlates of attentional switching, a family of negativities, called re-orienting negativity (RON) components, has been object of increasing interest across studies (Berti, Roeber, & Schröger, 2004; Berti & Schröger, 2001; Escera, Yago, & Alho, 2001; Schröger & Wolff, 1998a). Munka and Berti (2006) distinguished two components of RON. An earlier frontal negativity is elicited about 400-600 ms after a stimulus (Schröger, 2000; Schröger & Wolff, 1998a), whereas a later parietal and parieto-central negativity peaks roughly at 700 ms (Berti, 2008a). The early component was interpreted as a correlate of the "attentional refocusing as a working memory process in the sense of a switch of attention", while the later component was interpreted as a ''more general aspect of attentional allocation or evaluation after distraction (i.e., rehearsal of instruction or self-motivation)'' (Berti, 2008a, p. 609). At first, RON components were studied using distraction paradigms and were thought to reflect the subsequent refocusing of attention after the involuntary switch of attention triggered by a distracter stimulus (Berti, 2008b; Schröger & Wolff, 1998b). However, a recent study showed that the RON components were elicited not only after irrelevant stimuli, but also after relevant ones, suggesting that they might reflect a general index of attentional switching (Hölig & Berti, 2010). As far as

we know, only one study focused on the effect of aging on the RON, using an auditory distraction-paradigm (Horváth et al., 2009). Specifically, participants were required to perform a go/nogo duration discrimination task on a series of short and long (50–50%) tones. The elicited RON after distracter stimuli was resulted delayed by 80 ms in the older adults as compared to younger counterparts. The slowing-down of RON in elderly seems to indicate that the involuntary switching of attention required longer time in the elderly.

3.4 EXPERIMENT 2: INFLUENCE OF AGING ON ERP CORRELATES OF EXECUTIVE CONTROL PROCESSES

3.4.1 Introduction

It is well known that aging is accompanied by a decline in a wide number of cognitive domains, including episodic memory, working memory, problem solving and spatial abilities (e.g. Hedden & Gabriel, 2004, for an overview). A great challenge in research on cognitive aging is to identify a potential common and unifying factor that might account for this plurality of age-related deficits. Some explanatory factors have been proposed to be a reduction of attentional resources (Craik & Bosman, 1992; Craik, 1983), or a general slowing in information processing (i.e., 'The processing-speed theory'; Salthouse, 1996). Another possibility is linked to an enhanced susceptibility in elderly to interference due to an impaired ability to inhibit irrelevant information (Hasher & Zacks, 1988; Winocur & Moscovitch, 1983) (see Chapter 1, for a description of the main theories of aging).

As described in this chapter, the attention was recently drawn towards a dysregulation of executive control as potential mediator of age-related deficits, likely associated with changes in the prefrontal cortex (Braver & West, 2008; Raz, 2000; West, 1996). In particular, a computational theory of executive control proposed that older adults have deficits in the ability to represent, maintain, and update goal or contextual information in working memory ('Theory of cognitive control'; Braver et al., 2001; Braver & Barch, 2002; Braver & West, 2008). According to Braver & West (2008), age-related decline of goal maintenance produces decrements in several cognitive situations. The tasks that seem to be mainly sensitive to age are working memory tasks – where goal representations must to be maintained and updated over time– or inhibitory tasks, in which goal representations need to be used to inhibit or suppress inappropriate responses associated with goal-irrelevant perceptual dimension (Braver & West, 2008). This implicit idea of 'unity' among executive control processes has been alternatively corroborated by some studies (e.g., de Frias, Dixon, & Strauss, 2006; 2009) and challenged by others (e.g., Hedden & Yoon, 2006; Fisk & Sharp, 2004; Miyake et al., 2000, Luszcz, 2011, for a discussion on unity and diversity of executive functions). In particular, Miyake and collaborators (2000) showed, by using confirmatory factor analysis and latent variables, three different subprocesses belonging to executive control: shifting (or switching) between tasks or mental sets, updating information in working memory, and inhibition of prepotent responses.

A successive study (Fisk & Sharp, 2004) investigated the effect of aging on these subprocesses. The authors confirmed the Miyake's model, and observed age-related deficits on all of those factors that were interpreted as corresponding to updating, inhibition and shifting processes. Nonetheless, excepting for the age effect on shifting tasks, which displayed a less degree of attenuation, the age effects on updating and inhibition tasks resulted no longer significant after controlling for age-related differences in processing speed. In line with this finding, a recent review of meta-analyses (Verhaeghen, 2011) highlighted that, executive control, as a unitary construct, has a modest role in explaining age-related cognitive declines when taking into account also the speed of processing as mediator factor. He also reported that some specific processes of executive control (for example an inhibitory process called resistance to interference) did not show age-related deficits, whereas other ones (e.g., shifting-related processes as global task switching) were negatively affected by aging (see also Verhaeghen & Cerella, 2002).

The results described above highlighted how far we are from clearly understanding the mechanisms accounting for cognitive aging, and specifically the role of executive control as possible key explanatory mechanism for age decline. The present study took advance of the temporal resolution of event-related potentials (ERPs) to better investigate the effect of age on each specific subprocess composing the executive control (i.e., shifting, updating, inhibition). The task utilized to elicit the ERP components related to executive control was the Inhibitory Control Task (ICT; Garavan, Ross, Stein, 1999). During the ICT, a continuous stream of letters was presented, very quickly (i.e., for 500 ms without inter-stimulus interval), one after the other. In the first part of the task, participants were asked to respond by pressing a key only to the target letters (i.e., "X" and "Y,"). Trials containing a target letter were labelled as detect trials. In the second part, individuals were required to respond whenever the target letters were alternated (go trials), as when an "X" was preceded by a "Y", or *vice versa*, regardless of the irrelevant letters presented between them. In contrast, individuals had to withhold response if target letters were repeated (nogo trials), as when an "X" preceded another "X", or a "Y" preceded another "Y". The ICT seemed to be particularly suitable to study executive control since it involved all the executive subprocesses to be carried out. Specifically, an updating process was involved in order to know which target letter was previously presented. The inhibitory process was implied in nogo trials, in order to suppress prepotent responses when target letters were repeated (Garavan et al., 1999). Since the task was characterized by high time pressure,

individuals needed to rapidly shift attention from a trial to the next one. Therefore the attentional shifting was also required in this task. Given that detect trials did not imply either updating or inhibition, they involved the executive control to a lesser extent respect than the other two trial conditions, they might represent a good baseline condition. Indeed, according to the predictions formulated by the theory of cognitive control (Braver & Barch, 2002; Braver & West, 2008), or if conceptualizing the executive control as a unitary construct (e.g., de Frias et al., 2006), a greater age effect should be expected as the degree of executive control increased. Specifically, the age-related differences should be lowest in detect trials, intermediate in go trials and greatest in nogo trials, where both updating and inhibition processes were required.

We also investigated the effect of age on those ERP components mainly related to the three subprocesses of executive control. In this regard, the best-known ERP correlate of contextual updating is the P3b (Donchin & Coles, 1988; Kok, 2001; Polich, 2003; 2007). The P3b is a positive deflection elicited by task-relevant 'target' events and reaching its maximum amplitude over the parietal regions of the scalp. The peak latency of P3b occurs approximately 300 to 400 ms post-stimulus and is thought to reflect classification speed, which is proportional to the time needed to evaluate a target stimulus (Kutas et al., 1977; Magliero et al., 1984). Several studies have reported age-related changes in the P3b component elicited during a variety of paradigms (Friedman, 2003). In particular, aging was commonly associated with an increase of P3b latency and a decrease of P3b amplitude (e.g., Barrett, Neshige, & Shibasaki, 1987; Brown, Marsh, & LaRue, 1983; Fein & Turetsky, 1989; Fjell & Walhovd, 2003; Polich, 1996).

The electrophysiological indexes of response inhibition were usually examined through the use of "go/no-go" paradigms. Two ERP components were resulted more pronounced in nogo trials: the N2, expressed over central and fronto-central regions as a negative potential developing between 180 – 400 ms post-stimulus; and the nogo-P3, a positive deflection over central sites peaking between 300 and 600 ms post-stimulus (Falkenstein et al., 1999; Kok, 1986; Pfefferbaum, Ford, Weller, & Kopel, 1985; Simson, Vaughan, & Ritter, 1977). While the nogo-P3 has been consistently shown to reflect inhibitory processes (Kok et al., 2004; Ramautar et al., 2004), the functional significance of the N2 has been still debated. Indeed some studies showed that N2 reflects the conflict detection between opposite responses, rather than inhibition per se (e.g., Donkers & Van Boxtel, 2004). In line with this suggestion, a recent review highlighted that N2 components might

be interpreted as a general index of cognitive control (Folstein & Van Petten, 2008).

Only a handful of studies investigated the age effect on the ERPs elicited by go/nogo paradigms, leading to mixed results, especially regarding nogo-P3 amplitude. Indeed, some studies reported larger nogo-P3 in the young compared to older adults (e.g., Beste, Willemssen, Saft, & Falkenstein, 2010; Pfefferbaum, & Ford. 1988), whereas other studies reported equivalent, or even a higher nogo-P3 in older adults (e.g., Falkenstein et al., 2002; Vallesi et al., 2009; Vallesi, 2011). On the other hand, there is converging evidence of delayed peak latencies for both the N2 and nogo-P3 components in older adults (Fallgatter, Mueller, & Strik 1999; Horvath, Czigler, Birkas, Winkler, & Gervai, 2009; Pfefferbaum & Ford, 1988). These findings have been interpreted as reflecting a general slowing in processes speed with aging, rather than a specific impairment of inhibitory processes (Falkenstein et al., 2002; Vallesi et al., 2009).

Finally, in the present study great attention was directed on the neural indexes of shifting. We focused on a specific kind of shifting, called attentional or 'focus' switching (Cowan, 1999; Garavan, 1998; McElree, 2001; Oberauer, 2002; Verheagen & Basak, 2005). The starting point for describing attentional switching is the embedded-process framework of working memory (Cowan, 1999). According to this model, working memory is characterized by a hierarchical two-tier structure. It consists of a larger zone of long-term memory in which information is available, but not immediately accessible; and a smaller zone, called the focus of attention, which holds in an accessible state only a single element at a given time (Garavan, 1998; McElree, 2001; Oberauer 2002). When an element needs to be processed but resides in the zone outside the focus of attention, a switch of the attentional focus towards that element is required (Oberauer, 2002).

In this respect, a family of negative potentials, called re-orienting negativities (RON), has been proposed to reflect the reorientation of the attentional focus (Berti, 2008a; Berti, Roeber, & Schröger, 2004; Berti & Schröger, 2001; Escera et al., 2001; Munka & Berti, 2006; Schröger & Wolff, 1998a). The RON components were distinguished between an earlier frontal negativity elicited 400-600 ms after a distracting event (Schröger, 2000; Schröger & Wolff, 1998a), and a later parietal/ parieto-central negativity peaking roughly at 700 ms (Berti, 2008a), both usually appearing after P3 waves. Recently, the RON components were demonstrated to occur not only after irrelevant stimuli, but also after relevant ones (Hölig & Berti, 2010). This suggests that the RON represents a general index of attentional switching, and seems to be closely related to executive control (Berti, 2008a;

2008b; Hölig & Berti, 2010).

Attentional switching has gained an increasing interest as potential explanatory factor for the age-related deficits (Vaughan et al., 2008; Verhaeghen & Basak, 2005; Verhaeghen & Hoyer, 2007), nonetheless the relative ERP correlates have been poorly examined in the aging literature. As far as we know, only one study focused on the effect of aging on the RON, using an auditory distraction-paradigm (Horváth et al., 2009). This study showed that the RON components were delayed by roughly 80 ms in the older adults as compared to younger counterparts. Such slowing of the RON was interpreted to reflect a prolonged time required to elicit an attention switching in older individuals. However, an age-related change in the RON amplitude was not reported. As mentioned before, the ICT utilized in our study seemed to be a suitable task to examine the effect of age on the RON components. Indeed, since it was characterized by a high time-pressure with stimuli occurring very quickly it required participants to have an efficient reorientation of the focus of attention in order to be ready to process the upcoming stimulus.

Summarizing, the present study was aimed at spreading light on the role executive control in mediating the age-related declines in cognitive tasks. In particular, we considered – and hence investigated – the executive control from two different points of view, given the 'unity' and 'diversity' of its processes (Braver & Barch, 2002; Fisk & Sharp, 2004; Hedden & Yoon, 2006; Miyake et al., 2000, Salthouse, Atkinson, & Berish, 2003). First, we conceptualized the executive control as a unique and unitary construct. Therefore we expected to find an effect of age on ICT performance greater as the degree of executive control increased among the ICT conditions, thus lowest in the detect trials, intermediate in go trials and highest in nogo trials. Second, we investigated the age effect on each distinct subprocess composing executive control, focusing on their ERP correlates. To this end, we examined the P3b, the RON and the nogo-P3 since they reflect updating, shifting and inhibition processes, respectively. Furthermore, the P3a as well as the N2 components were investigated given their functional meaning related to executive control processes (Berti, 2008b; Folstein & Van Petten, 2008).

Finally, in order to better dissociate the effect of aging on the ERP components related to the each distinct process of executive control, a partial least square (PLS) analysis was run (McIntosh, Bookstein, Haxby, & Grady, 1996; Lobaugh, West, & McIntosh, 2001). PLS analysis is a multivariate statistical technique able to identify differences in ERP amplitude and latency across experimental conditions. (Lobaugh et al., 2001). This

technique is particularly useful when multiple processes are implied and may lead to a possible overlap among their ERP correlates, as in the ICT (e.g., updating and inhibition processes in nogo trials). Notably, previous studies showed that PLS analysis could effectively highlight the age effects on a single ERP component, or on more components of the ERPs that are different in topography (West & Moore, 2005; West & Schwarb, 2006; West & Travers, 2008).

3.4.2 Methods

Participants

Thirty-three participants were recruited, all were right-handed, reporting normal hearing and normal or corrected-to-normal visual acuity. None of the participants had neurological or neuropsychiatric disorders, and significant cardiovascular, respiratory or renal impairment. Seventeen were classified as young adults (age: 25 ± 4 years, mean ± SD; 7 females; education level 16 ± 2 years) and sixteen as old adults (age: 67 ± 5 years; 8 females; education level 13 ± 4 years). All participants completed a battery of psychometric tests, including Mini Mental State examination (Folstein, Folstein, & McHugh, 1975) TMT-A, TMT-B, Symbol-Digit test (Amodio, Montagnese & Gatta, 2004), in order to exclude neuropsychological disorders. Informed consent was obtained from all participants.

Stimuli and Procedure

Participants were seated in a semi-dark and quite room facing a monitor placed 83 cm from their eyes. The ICT was administered immediately after the psychometric evaluation by means of the E-prime software (E-Prime; Psychological Software Tools). Black letters were presented, one after the other, in the centre of a white background computer screen. In order to obtain a task with high time pressure, the letters were presented for 500 ms without inter-stimulus interval. Interspersed within the other letters, the target letters "X" and "Y" occurred. During the first part of the task, the participant was instructed to respond (pressing the space bar of the computer keyboard) to every "X" and "Y" ("detect trials"). During the second part of the task, the participant was instructed to respond only when "X" and "Y" were alternating (i.e., "go trials") and to withhold response when "X"

and “Y” were repeated (i.e., “nogo trials”). In other words, the participant was instructed to respond only if an “X” was preceded by a “Y” or a “Y” was preceded by an “X”. Responses must be inhibited if an “X” was preceded by an “X” or a “Y” preceded by a “Y”. The first part, divided in two blocks, was composed by 500 letters, 75 of which were detect trials. The second part consisted of 6 blocks of trials, for a total of 1753 letters, 254 of which were go trials, and 47 were nogo trials. In line with the original version of the task (Amodio et al., 2010; Bajaj et al., 2007; Garavan et al., 1999), we decided to administer always the first part with the detect trials at the beginning, and then the go/nogo task. The choice was made to prevent any possible tendency to inhibit the response in the detect trials. Similarly, we decided to maintain the same proportion of go and nogo trials used in the original version of the task. Although this could influence the amplitude of some ERPs, for example the P3b (e.g., Johnson & Donchin, 1982), nonetheless it made the nogo trails an effective inhibitory condition. Indeed we were mainly interested in identifying possible deficits related to a given cognitive function rather there in comparing the same ERP component (e.g., P3b) in the different trial conditions. A practice block was run in order to make participants confident with the go/nogo task.

Behavioural analysis

The percentage of accuracy was obtained for detect, go and nogo trials and was analysed through a 3 × 2 ANOVA with trial type (detect vs. go vs. nogo trial) as the within subject factor and age group (young vs. elderly) as the between subjects factor. To assess response speed, RTs in detect and go trials were analysed by means of a 2 × 2 ANOVA with trial type as the within subject factor and age group as the between subjects factor. When required, post-hoc analyses were done with Bonferroni correction. Partial eta-square (η^2) values were calculated for all ANOVAs as an effect size index.

Electrophysiological recording and pre-processing

EEG activity was recorded (EEG equipment: System Plus, Micromed, Italy) from an array of 31 Ag/AgCl electrodes: Fp1, Fp2, AF3, F4, F7, F3, Fz, F4, F8, FC5, FC1 FCZ, FC2, FC6, T7, C3, Cz, C4, T8, CP1, CPZ, CP2, P7, P3, PZ, P4, P8, O1, O2 (Brainquick 3200; Micromed, Mogliano Veneto, Italy). A standard pre-cabled electrodes cup was used, and the electrodes placed according to the 10-20 international system. The ground was placed on Fpz (midline fronto-polar derivation) and the reference was the linked mastoids.

Impedance was kept under 5 kΩ. Each channel had its own analogue-to-digital converter, and signals were digitally filtered with a pass band filter of 0.33-60 Hz. The sampling frequency was 512 Hz, the conversion resolution was 0.19 mV/digit. Two electrodes were used to record vertical and horizontal eye movements. Data processing was performed under Matlab (Version 7.4.0, MathWorks, Natick, MA, USA) using the EEGLAB 8 toolbox (Delorme and Makeig, 2004). The EEG data were offline downsampled at 256 Hz and filtered with a 30 Hz low-pass filter. Epochs were locked on the presentation of the letters. ERP analysis epochs included 500 ms of pre-stimulus baseline and 1500 ms post-stimulus activity, and corrected to the pre-stimulus baseline (time-window ranging from -500 to 0 ms) . Artefact correction was made by using the Independent Component Analysis (ICA) (Onton et al., 2006). The data were re-referenced to an average reference. Epoch rejection was performed with a cut-off of ± 75 μV. Only epochs with correct response were analysed. The final ERP analysis was based on a mean of 89% of the epochs relative to the original number of epochs.

ERPs analysis

The analysis focused on those ERP components that were commonly shown to be related to the studied processes, namely: N2, P3b, nogo-P3, and RON. The choice of the derivations for the analysis were driven by the literature about scalp distribution of these ERPs, by visual inspection of the main differences between the two age groups, as well as by the findings obtained from Partial Least Square (PLS) Analysis (see below, for details on PLS analysis).

We investigated the age-related differences on latency and amplitude of a positive-negative-positive succession of peaks over the lateral frontal regions by means of three 2 × 3 × 2 ANOVAs with derivation (F7 vs. F8) and trial type as within subjects factors, and age group (young vs older adults) as between subjects factor. Specifically the ANOVA was run on the latency and peak amplitude of P3a (time-window: 180-500 ms post-stimulus), frontal RON (250-900 ms), and slow wave positivity (700-1100 ms).

Moreover, the age effect was studied on the peak latency and amplitude of the N2 (150-600 ms post-stimulus) and nogo-P3 (300-800 ms post-stimulus) complex by a 3 × 3 × 2 ANOVA considering the derivation (Cz, C3 and C4), trial type and age group age as factors. Finally an ANOVA analysis with the same factors was run on the P3b (300-800 ms) and the parietal RON (600-1100 ms), considering Pz, P3 and P4 as the levels of the

derivation factor.

Post-hoc contrasts were performed to explore the significant effects evidenced by ANOVAs. When sphericity was violated (i.e., when the Mauchley sphericity test was significant), the Huynh and Feldt correction (1976) was applied. Partial eta-square (η^2) values were calculated for all ANOVAs as an effect size index.

Partial Least Square analysis

Partial Least Square (PLS) analysis is a multivariate data analysis technique that allows one to identify spatiotemporal relationships between neural activity and experimental design (Alin, Kurt, McIntosh, Öniz, & Özgören, 2009; Lobaugh et al., 2001; McIntosh et al., 1996). Its primary advantage over other multivariate techniques used for EEG analysis (as Principal Component Analysis, PCA, or Independent Component Analysis, ICA) is that it is designed to identify where, simultaneously in space and time, the strongest experimental effects are expressed. PLS is the elective tool for our aims because it is able to identify the ERP effects related to the experimental manipulations, and dissociate them from other possible confounding factors.

The term *Partial Least Square* refers to the computation of the optimal least-squares fit to part of the correlation or covariance matrix of data (Lobaugh et al., 2001). In this experiment the part is the "cross-block" correlation between the exogenous variables (i.e. the experimental conditions) and the dependent measures (i.e. the ERP amplitude). The PLS analysis included six task conditions obtained by crossing the 3 trial type × 2 Age group levels.

The ERP input data matrices for the PLS analyses contained subjects and conditions in the rows, and ERP amplitudes for all time points and channels, except for the two ocular electrodes, in the columns. Analysis was restricted to post stimulus interval, from 0 to 1000 ms. As first step the input data matrices were transformed by mean-centering the columns of the ERP data matrix with respect to the grand mean. The averages within each condition were therefore expressed as deviations around zero. The matrix underwent Singular Value Decomposition (SVD) to yield a set of latent variables (LVs). Each LV describes how strongly a certain pattern of experimental conditions (design scores) are expressed by each electrode at each time point (electrode saliences).

Specifically three outputs were derived from the SVD that serve to interpret the relationships between ERP amplitude and experimental conditions. The first was a vector

of singular values, which represents the unweighted magnitude of each LV and is obtained to calculate the proportion of the cross-block covariance matrix (i.e., the percentage of task-related variance) attributable to each LV. The second and third outputs contained the structure of the LVs and are orthogonal pairs of vectors (saliences) that are used to identify the temporal and spatial of the latent variables.

The significance of the latent variables singular values was yielded using a permutation tests (1000 replications). Permutations consist of sampling without replacement to reassign the order of conditions for each subject. PLS is recalculated for each new permuted sample, and the number of times the permuted singular values exceeded the observed singular value in each LV is calculated as a probability. A LV was considered significant at $p < 0.05$. To prevent the effects of possible outliers, the stability of the ERP saliences in space and time was established through bootstrap resampling (200 replications) that provides a standard error. Bootstrap ratios greater than 2.5 were chosen as the cut-off for stable non-zero saliences. The main purpose of the bootstrap procedure is to clarify those portions of the ERPs that express relevant experimental effects across subjects. Matlab code to perform the PLS analyses can be downloaded at http://www.rotman-baycrest.on.ca/pls.

3.4.3 Results

Behavioural results

The analysis on the percentage of accuracy evidenced that the performance was lower in nogo trials as compared to the other types of trials for both the young and older adults, and that the older adults performed worse than the young counterparts in all the types of trials. Indeed the age group × trial type ANOVA revealed a significant main effect of the trial type [$F(2,62)=21.83$; $p< .01$, $\eta^2=0.41$], with a lower percentage of accuracy for nogo trials (83% mean ± 10 SD) as compared to both detect (95 ± 6 %) and go trials (93 ± 7 %), all ps<.01. The main effect of age group was significant [$F(1,31)=9.03$; $p< .01$, $\eta^2=0.22$] with a lower percentage of accuracy in the performance of the older adults (88 ± 10 %) than that of the young adults (93 ± 5 %), regardless of the type of trial considered. The interaction between age group and trial type was not significant. Likewise, the ANOVA on RTs revealed a significant effect of trial type [$F(1,31)=36.56$; $p< .01$, $\eta^2=0.54$] and age group

[F(1,31)=30.91; p< .01, η^2=0.49]. RTs were delayed in go trials (532 ± 46 ms) than in detect trials (500 ± 41 ms). Moreover RTs were slower for the elderly group (557 ± 54 ms) as compared to young group (475 ± 33ms), in both the two types of trials. The interaction age group × trial type was not significant.

Both the findings on percentage of accuracy and RTs converged in revealing that the elderly group showed impairments in the performance of the ICT, in all the types of trials studied. This suggested that the age-related changes in the ICT performance occurred regardless of the degree of executive control required for a given trial.

ERP results

Visual inspection showed that the main ERP components (e.g., N2, P3b, RON) were delayed in the elderly group if compared to the young group, regardless of the type of trial. Moreover the latency of these ERPs were influenced by the type of trial, being delayed in nogo trials.

Given these considerable latency shifts, the amplitude of the ERP maximum peak (e.g., for the P3b) or minimum peak (e.g., for the N2), was analysed within a large time-window.

A shift of all the ERPs investigated was found for older adults, as compared to younger adults, in both detect, go and nogo trials. A difference in terms of ERP peak amplitude between the two groups seemed to be mainly expressed in the later ERPs, such as the RON and the frontal slow waves, with the older participant showing a reduction in the amplitude of these components. Interesting, we found not only an earlier frontal RON, but also a later RON, expressed over the parietal and centro-parietal regions, both of them sensitive to the age of the group and to the type of trial (see Figure 3.3 and Figure 3.4).

P3a

The ANOVA analysis on P3a latency over frontal derivations (F7 vs F8) revealed a significant effect of age group [F(1,31)=7.73; p< .01, η^2=.20], with the P3a being delayed for older than younger adults. Moreover the trial type × derivation interaction was significant [F(2,62)=3.80; p< .05, η^2=.11]. Post-hoc analyses revealed that a difference in the P3a latency between go and nogo trials was significant in F7, with nogo trial having a longer P3a (all ps < .05). Whereas the trial type × age group interaction was not significant.

Concerning the analysis of peak amplitude, the main effect of trial type [F(2,62)=4.25; p< .05, η^2=.12] and the derivation [F(1,31)=11.38; p< .01, η^2=.27] were significant, as well

as trial type × derivation interaction [$F(2,62)=6.19$; $p< .01$, $\eta^2=.17$]. Post-hoc analyses evidenced that ERPs were greater in go and detect trials respect than nogo trials, in F8 (all ps < .05). In contrast, neither the main effect of age group nor the trial type × age group interaction were significant.

In summary, the P3a was delayed in older adults respect than younger adults, and it was more positive in go and detect trials than in nogo trials, especially over the right frontal sites (F8).

Frontal RON

The ANOVA on latency of RON over frontal sites (F7, F8) revealed the significant main effect of age group [$F(1,31)=8.48$; $p< .01$, $\eta^2=.21$], with the RON being delayed for older than younger adults. The effect of trial type was also significant [$F(2,62)=8.45$; $p< .01$, $\eta^2=.21$], specifically nogo trials were characterized by a later RON (Figure 3.3), if compared to both go and detect trials (all ps<.01). The interaction between trial type and age group was not significant.

The ANOVA on peak RON amplitude evidenced that the trial type × derivation interaction [$F(2,62)=3.65$; $p< .05$, $\eta^2=.11$] was significant. Specifically in F8, this negative component was smaller in go trials respect than detect and nogo trials. Furthermore the trial type × age group × derivation interaction was significant [$F(2,62)=3.37$; $p< .05$, $\eta^2=.10$]. Indeed in the right frontal region (F8), the RON was more negative in detect trials than in go trials for the young group, whereas it was more negative in nogo trials than in go trials for the elderly group (all ps < .05). On the other hand the RON amplitude in F7 was not influenced by either the trial type or age group considered.

In summary, the latency of the frontal RON was sensitive to the age group, being delayed for the older adults, and to the trial type considered, being delayed in nogo trials than the other two types of trials. Furthermore, the amplitude of this component seemed to be influenced by the trial type and the age of the group, especially over the right frontal regions. Anticipating the PLS results, we showed that another frontal negativity, lateralized over right hemisphere, overlapped the RON and was mainly related to inhibitory processes.

Frontal slow wave

The ANOVA on the latency of frontal slow wave showed that the main effects of trial type [$F(2,62)=11.84$; $p< .01$, $\eta^2=.28$] and age group [$F(1,31)=8.72$; $p< .01$, $\eta^2=.22$] were significant. These effects indicated that frontal slow wave was delayed for older than younger adults, and delayed in nogo trials than the other two types of trials (ps<.01). Again, the interaction between these two variables was not significant. The same ANOVA on peak amplitude evidenced the significant main effects of trial type [$F(2,62)=10.16$; $p< .01$, $\eta^2=.25$], derivation [$F(1,31)=5.83$; $p< .05$, $\eta^2=.16$], as well as age group [$F(1,31)=18.25$; $p< .01$, $\eta^2=.37$], with a reduced frontal slow wave for older compared to younger adults, as can be seen in Figure 3.3. Moreover the trial type × derivation interaction was significant [$F(2,62)=4.09$; $p< .05$, $\eta^2=.12$]. Post-hoc analysis suggested that detect trials had a greater frontal slow wave compared to go trials (in both the F7 and F8), and also to nogo trials in F8 (ps< .01).

In summary, the frontal slow wave component resulted delayed and less positive for older than younger adults. It was also influenced by the type of trials being slower in nogo trials respect than the other two types of trial. Finally it was greater in detect than in go and nogo trials, especially when analysed in F8.

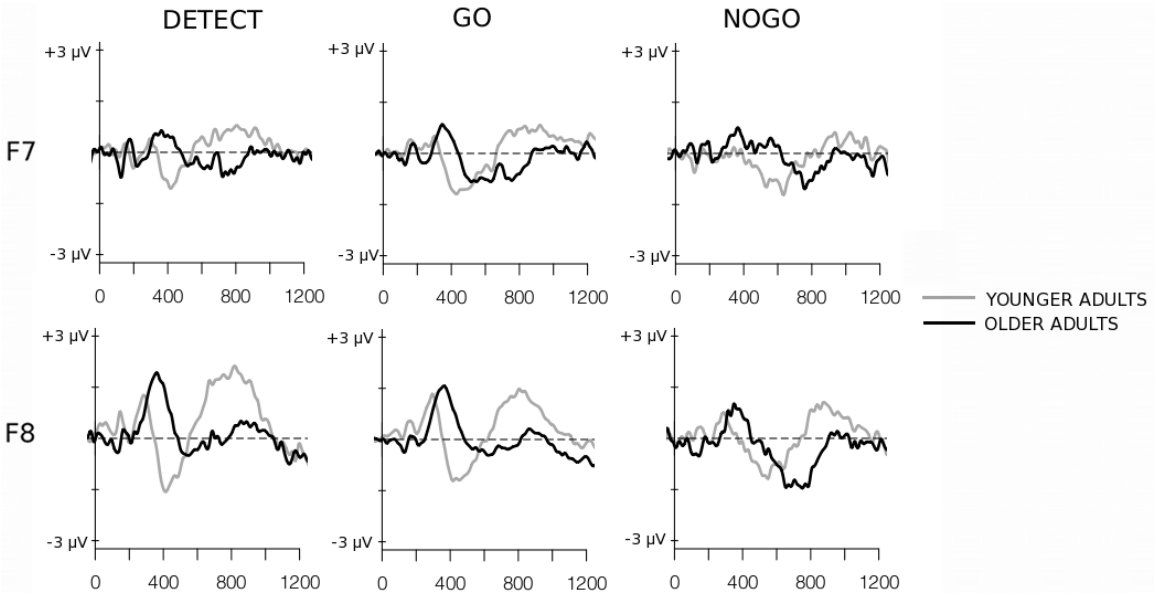

Figure 3.3 Grand average ERP waveforms in younger and older adults over lateral frontal sites. The plots show the ERPs of younger adults (gray line) and older adults (black line) of the F7 and F8 derivations), separately for detect, go and nogo trials.

N2

The ANOVA on the latency of the N2, analysed over central sites (Cz, C3, C4) evidenced the significant main effects of age group [$F(1,31)=10.07$; $p< .01$, $\eta^2=.25$] and trial type [$F(2,62)=3.38$; $p< .05$, $\eta^2=.10$]. The age group did not interact significantly with the type of trial, showing that the delay of the N2 for older adults occurred regardless of the trial considered (Figure 3.4). The trial type × derivation interaction was significant [$F(2,62)=5.94$; $p< .05$, $\eta^2=.16$], revealing that in C4 derivation, N2 was delayed in nogo trials than in the other two types of trial (all ps <.01).

Concerning the N2 peak amplitude, the following effects were significant: trial type [$F(2,62)=9.05$; $p< .01$, $\eta^2=.23$], derivation [$F(2,62)=23.77$; $p< .01$, $\eta^2=.43$], the trial type × derivation interaction [$F(4,124)=12.05$; $p< .01$, $\eta^2=.28$] and the trial type × age group interaction [$F(2,62)=3.51$; $p< .05$, $\eta^2=.10$]. This last interaction indicated that the N2 was more negative in detect compared to go trials (for both the age groups), and also compared to nogo (only for older adults), all ps <.05. Finally the trial type × age group × derivation interaction was significant [$F(4,124)=4.88$; $p< .01$, $\eta^2=.14$], showing that the N2 over Cz was more negative for older adults than for younger adults, only in go trials, all ps <.05.

Summarizing, the N2 was always delayed in older adults respect than younger adults, regardless of the trial type considered; moreover it was more negative in older compared to younger adults when it was analysed in Cz, only in go trials.

Nogo-P3

For the analysis of the nogo-P3, the central derivations (Cz, C3, C4) were considered. The ANOVA on latency revealed the significant effect of trial type [$F(2,62)=17.90$; $p< .01$, $\eta^2=.37$], with nogo trials characterized by a delayed P3 than the other two types of trial (all ps<.01), and of the age group × derivation interaction [$F(2,62)=4.45$; $p< .05$, $\eta^2=.13$]. Such an interaction indicated that the nogo-P3, expressed over C3 derivation, was delayed in older adults respect than younger adults, regardless of the trial considered (all ps < .05). Again, the interaction between age group and trial type was not significant.

Concerning the peak amplitude, the nogo-P3 was significantly influenced by the trial type [$F(2,62)=4.04$; $p< .05$, $\eta^2=.12$], being higher in nogo than the other two trial types (all ps <.05); and derivation [$F(2,62)=9.34$; $p< .01$, $\eta^2=.23$]. Moreover the trial type × age group interaction was significant [$F(2,62)=3.61$; $p< .05$, $\eta^2=.10$]. Post-hoc analyses indicated that nogo-P3 was higher in nogo trials than in go trials for older adults, but not

for younger adults, all ps < .01. Nevertheless a difference in the nogo-P3 amplitude between young and older adults was not significant (p>.05). The trial type × derivation interaction resulted significant [$F(4,124)=3.86$; $p< .01$, $\eta^2=.11$]. Indeed go trials showed a lower nogo-P3 as compared to detect trials (in Cz), and also compared to nogo trials (in C3), all ps < .01.

In summary, the latency of the nogo-P3 was delayed for older respect than younger adults in all trial types (Figure 3.4); and it was slower in nogo trials respect the other trials. The peak of the nogo-P3 was higher in nogo trials than go trials, especially for older adults and over C3 derivation.

P3b

The analysis of the P3b focused on parietal regions (P3, Pz, P4), and revealed that the P3b latency was significantly influenced by age group [$F(1,31)=21.91$; $p< .01$, $\eta^2=.41$], being delayed for older than younger adults (Figure 3.4), and by trial type [$F(2,62)=27.60$; $p< .01$, $\eta^2=.47$], being slower in nogo than the other two trial types (all ps < .01). Likewise for the other components, also for the latency of the P3b there was not a significant interaction between age group and trial type. The ANOVA on the P3b amplitude evidenced a significant effect of derivation [$F(2,62)=6.16$; $p< .01$, $\eta^2=.17$]. Moreover, the trial type × derivation interaction [$F(4,124)=3.11$; $p< .05$, $\eta^2=.09$] and the trial type × age group × derivation interaction [$F(4,124)=2.54$; $p< .01$, $\eta^2=.08$] were significant. Post-hoc analyses exploring this last interaction showed that P3b, recorded over Pz derivation, was less positive in nogo trials than in the other two trial types, only for younger adults (all ps<.01). Whereas it was not different depending on the trial type for older adults, the P3b amplitude was not significantly different between young and older adults.

Summarizing, the P3b was delayed for older adults, regardless of the trial type; and was delayed in the nogo trial compared to the other two trial types (for both the young and the older adults). The trial type influenced the amplitude of the P3b only for younger adults, especially when Pz site was considered.

Parietal RON

The ANOVA on the parietal RON latency focused over Pz, P3 and P4, and revealed a significant effect of the age group [$F(1,31)=4.70$; $p< .05$, $\eta^2=.13$], being delayed for old than young adults.

The ANOVA on amplitude of the parietal RON revealed that all the main effects were significant: age group [$F(1,31)=30.01$; $p< .01$, $\eta^2=.49$], with old adults showing a less negative RON respect than young adults (Figure 3.4); trial type [$F(2,62)=10.06$; $p< .01$, $\eta^2=.25$] and derivation effect [$F(2,62)=17.88$; $p< .01$, $\eta^2=.37$]. Moreover the trial type × derivation interaction was significant [$F(4,124)=6.44$; $p< .01$, $\eta^2=.17$]. Indeed the RON was more negative in detect compared to go trials (for all derivations), and also compared to nogo trials when recorded over P3 (all ps <.01).

Interestingly, the parietal RON was delayed and less negative for old than for young adults, and the amplitude of its peak was influenced by the trial type being more negative in detect trials than in the other trials (for both the age groups).

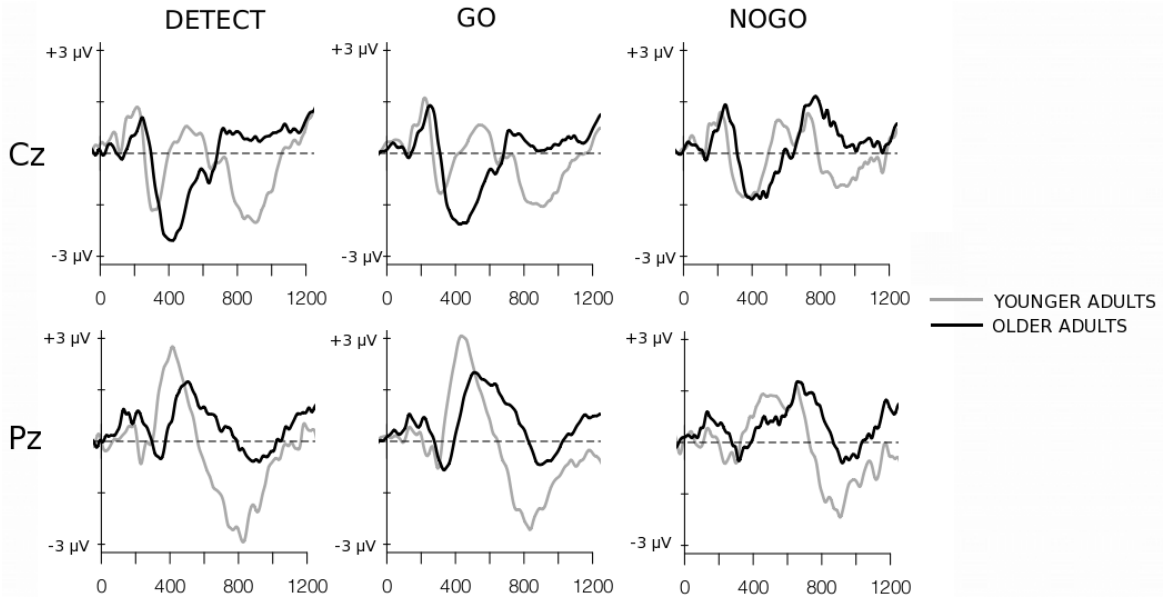

Figure 3.4 Grand average ERP waveforms in younger and older adults over midline central and parietal sites. The plots show the ERPs of younger adults (gray line) and older adults (black line) of the Cz and Pz derivations), separately for detect, go and nogo trials. Since no remarkable between-hemisphere differences in age effects were found, only midline derivations are reported here.

Results from Partial Least Square Analysis

The PLS analysis allowed us to better clarify the main ERP correlates of the processes investigated in the two age groups. The permutation test revealed three significant latent variables.

The first LV ($p < .00001$), which accounted for 55.38% of the crossblock covariance matrix (Figure 3.5) distinguished the nogo trials from detect and go trials, in both the

young and old adult groups. Therefore, this LV captured the ERP components associated with the inhibitory processes. The electrodes salience reflected a delayed positivity over central, centro-parietal and parietal regions, which presumably indicated the nogo-P3. Moreover such a nogo-P3 component was coupled with a negative wave over frontal and frontopolar regions (e.g., F8, Fp2, AF4), lateralized over the right hemisphere, and occurring roughly in the same time-window of the nogo-P3 (400-500 ms). This negative deflection has been highlighted in the previous ANOVA analysis on the ERPs over F7 and F8 and might have been confused with the frontal RON. PLS analysis was helpful to dissociate these two overlapping components: the frontal RON (associated with attentional shift) and another negative deflection mainly related to inhibitory processes (Figure 3.5).

The second LV ($p<.0001$) that accounted for 26.43% of the crossblock covariance matrix distinguished the the go trials from detect and nogo trials (Figure 3.5). Specifically in the young group, the contrast was mainly between go and detect trials, whereas in the group of older adults it was mainly between go and nogo trials. This LV seemed to capture mainly the ERP components associated with the updating processes, similarly expressed by young and older adults. The ERP activity more related to go trials, as evidenced by the electrode salience, was an increased negativity followed by an increased positivity over parietal regions, which seemed to be a modulation of the N2 and P3b, respectively. Moreover, such LV was expressed in an enhanced negativity over left frontal regions at 400 ms coupled with an enhanced positivity over occipital and temporo-parietal lobe, at approximately the same time window.

The third LV ($p<.015$) accounted for the 13.03 % of the cross-block covariance and contrasted the same type of trials between the two age groups (Figure 3.5). Therefore, this LV seemed to express the main differences in the ERP waveforms between younger and older adults. Specifically the electrode salience reflected a general latency shift of the ERP components in older adults. This shift seemed to involve several ERPs extensively over the scalp: starting from the N2 over occipital and parietal regions, to the P3a over central, fronto-central, frontal and prefrontal regions, and the P3b over parietal and centro-parietal regions.

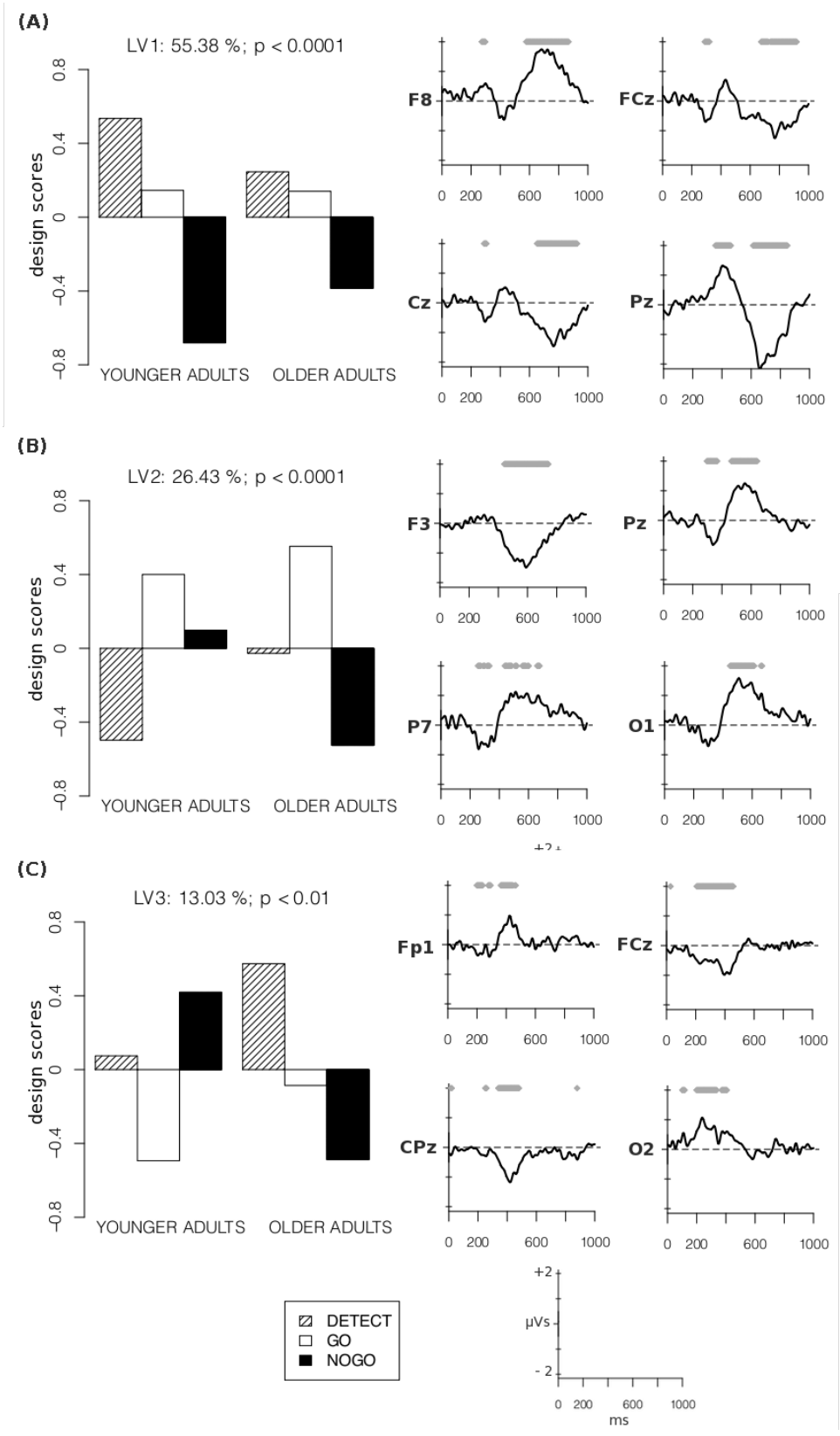

Figure 3.5 Results of the PLS analysis contrasting detect, go, and nogo trials in younger and older adults. (A) The first LV reflecting the neural correlates of inhibition in both the younger and older adults. (B) The second LV reflecting the neural correlates of updating in the younger and older adults. (C) The third LV reflecting the differences between the younger and older adults, mainly expressed as delay in ERP latencies.

3.4.4 Discussion

Different theories tried to identify a common mechanism able to explain for the plurality of cognitive deficits in aging. Recently, the executive control has been proposed as a possible key mediator of this age-related decline (Fisk & Sharp, 2004; Braver & Barch, 2002; Braver & West, 2008). In particular, according to the theory of cognitive control (Braver & Barch, 2002; Braver & West, 2008), the age-related impairment of executive control would produce specific decrements in those cognitive tasks that are more demanding for this function. In order to test this prediction, the present study adopted the inhibitory control task (ICT), which consisted of trials requiring an increasing demand of executive control. The age effect was expected greater in the ICT trials requiring a higher degree of control (e.g., in nogo trials). Nevertheless, behavioural data revealed that older adults had a worse performance respect than younger counterparts in all the types of trials, as from detect trials to nogo trials, regardless of the amount of executive control needed. As compared to younger adults, older adults showed a slowing of RTs not only in go trials, but already in detect trials. Importantly, the age effect on performance did not interact with the type of trial, being independent from the degree of executive control required to perform them. Therefore, when conceptualized as unitary factor, the executive control was not able to account for the age-related differences on ICT performance. This finding suggests that executive control does not seem to be the elective factor for explaining age-related deficits. Although suggestive, this conclusion might be subject to criticisms, for example because it was driven by a null interaction. In this regard, the use of the ERP technique might be helpful to clarify the mechanisms responsible for the age-related deficits in the ICT. Specifically, we investigated the effect of age on the ERP components associated with each subprocess of executive control (i.e., inhibition, updating, shifting).

First of all, we observed a delay of the ERPs in older adults. Such a delay concerned all the ERPs investigated and was shown in all the types of trial, thus regardless of the degree of executive control as well as the process required for completing that trial. The slowing of the ERP latencies was also reflected in the third LV of PLS analysis. Indeed, it was worthy of note that the major difference captured by this LV was a general delay in the ERPs, not related to a particular type of trial. In agreement with the findings from the ANOVA, the age-related alterations revealed by the third LV involved a wide number of ERP components, including the early (e.g., P1, N2, P2 components) and the later components (e.g., P3b), and expressed over all the regions of the scalp (as from prefrontal

to occipital sites). As for the behavioural results, also the findings on the ERP latencies cannot be explained by an age-related difference in executive control. Rather, they might reflect a general slowing of processing speed in elderly individuals. This pattern of results gave support to the Salthouse's theory (for a review, see Salthouse, 1996), which assumed that age-related cognitive decline is due to a general reduction in the speed of cognitive processes. Moreover, our study corroborated the findings derived from a recent review of meta-analyses (Verhaeghen, 2011), which concluded that the general construct of executive control "does not explain any age-related variance in complex cognition over and beyond the effects explained by simple speed of processing" (Verhaeghen, 2011).

Focusing on the electrophysiological correlates of the single process investigated, the first LV of PLS analysis captured the ERP activity specifically related to inhibitory processes. This LV revealed that similar ERP patterns underpinned inhibitory processes in the two age groups. In line with the literature, the first LV highlighted the nogo-P3, a positive component that has been consistently interpreted as an index of inhibition (e.g., Falkenstein et al., 1999; Pfefferbasum et al., 1985). The nogo-P3 was delayed in the older adults, nevertheless it did not differ respect the nogo-P3 observed by young adults in terms of peak amplitude. The influence of aging on the nogo-P3 is still debated, with some studies showing an attenuation of the nogo-P3 amplitude with age (e.g., Pfefferbaum & Ford, 1988) and others reporting equivalent amplitudes between the two age groups (Falkenstein et al., 2002). This pattern of results might be taken as a further evidence of a general slowing in older adults, rather than a specific deficit of inhibition, as also proposed by other ERP studies on inhibition (Falkenstein et al., 2002; Rush et al., 2006; Vallesi et al., 2009). Interestingly, the first LV showed that nogo trials were also characterized by an increased negativity, lateralized over the right frontal regions and starting roughly 400-500 ms post-stimulus, in a similar time-window of the nogo-P3. Since this frontal negativity was captured by the same LV that evidenced the no-go P3, therefore it seemed to be as well a neural correlate of response inhibition. The topographical distribution of the negative wave corroborated this idea. Indeed several neuroimaging studies, and especially an fMRI study that used the same paradigm (Garavan et al., 1999), identified the right frontal gyri (i.e. inferior frontal gyri) as crucial regions for inhibitory control (Chambers et al., 2009, for a review). This negative wave was shown in the ANOVA, but was overlapped by the frontal RON. Therefore, it was difficult to clarify in which way the age affected RON and this inhibition-related negativity, respectively. The ANOVA evidenced that older adults had

a delayed frontal negativity, but particularly pronounced in nogo trials. This result could be interpreted as reflecting an age-related compensatory mechanism in order to cope with the difficulties in inhibiting the response.

It was surprising to notice that N2 was not captured by the first LV. On the contrary, the N2 was expressed in the electrode salience of the second LV, which distinguished go trials from the other two trial types. Therefore the second LV seemed to reflect the ERP components mainly related to the updating process. This result might corroborate the claim that N2 is not a specific correlate of inhibition but, rather, it occurs whenever executive control has to be exerted in order to select an adequate response, as in go trials (i.e., 'the conflict account'; Botvinick et al., 2001; Folstein et al. 2011, Randall & Smith, 2011). The comparison between the two groups in the N2 amplitude highlighted that in go trials, the N2 was delayed but more negative in older adults than in younger adults. This finding is interesting since it is opposite to the previous researches, which showed attenuation, instead of an enhancement, of the N2 in older adults (Riis et al., 2008; Muller & Knight, 2002; Snyder & Hillyard, 1979). Since the N2 is sensitive to cognitive control, as reviewed by Folstein and Van Petten (2008), the larger N2 in older adults could indicate that they compensated with the difficulties of the task by recruiting more controlled resources, in agreement with the most recent theories of compensatory processes in aging (Cabeza et al., 2002; Daffner et al., 2006; Duarte et al., 2006; Park & Reuter-Lorenz, 2009; Riis et al., 2008: Stern, 2002). Furthermore, such suggestion was driven by the evidence obtained in another study of our research group which employed the ICT to investigate the ERP alterations linked to minimal hepatic encephalopathy, a neuropsychological condition due to liver cirrhosis (MHE; see Experiment 4, in Chapter 4). Indeed, if compared with the N2 of controls, the N2 of cirrhotic patients was less negative in those patients with MHE, but more negative in the group of patients without MHE, who were patients that had adequate compensatory mechanisms for coping their covert brain dysfunctions. Nonetheless, though appealing, this interpretation has to be specifically tested in future studies, maybe investigating the changes in the N2 depending on the inter-individual differences of performance in older individuals.

As expected, the second LV captured the P3b, the typical index of updating (e.g., Polich, 1996; Kutas et al., 1977; for a review, Polich, 2007). As for the no-go P3, also this component resulted delayed, but not significantly attenuated in older adults respect in younger adults, suggesting somehow preserved updating processes in aging.

Another crucial issue of the present study consisted in investigating the effect of aging on the RON components (Berti, 2008; Hölig & Berti, 2010; Schröger &Wolff, 1998a). Coherently with the literature, also our study revealed two different RON components: an early frontal negativity, and a later parietal negativity (Berti, 2008b). Both of them resulted influenced by the age of group, being delayed and less pronounced (especially the parietal RON) in the elderly group. The only other study that has investigated the age-related alterations on the RON components utilized an auditory distraction-paradigm and reported a slowing of the RON with age (Horváth et al., 2009). The present study extended the results obtained in the work by Horváth suggesting that the age-related impairment of attentional switching occurred not only after distracter stimuli, but also after task-relevant ones. It seemed that in older adults, switching mechanism of attention took longer and was more difficult, probably because they were still engaged in processing the previous stimulus. Thus, the analysis of the RON components, in a paradigm with high time pressure such as the ICT, highlighted that an age-related decline was shown in one subprocess of executive control, namely the switch of attention (Cowan, 1999; Oberauer, 2002; Verheagen & Basak, 2005). Indeed the RON was not only delayed, but also less negative in older adults. This alteration cannot be simply accounted by a general slowing of processes, but may reflect a specific deficit in attentional switching. The present finding might mirror the pattern of results obtained in the study by Fisk and Sharp (2004). Indeed these authors reported that, when taking into account the differences in processing speed between the age groups, the effect of age on performance was still significant only in shifting tasks (but not in updating or inhibition tasks).

Hence, our study developed the knowledge about the relation between the RON and executive control (Berti, 2008a), showing how this component was sensitive to the degree of executive control implied in the trial. The parietal RON, especially over left regions, was larger in detect trials than in the other trials. Similarly, also the frontal RON was more pronounced in detect trials respect than in go trials (especially over right regions). In general, the greater RON components after low executive control demanding trials (i.e., detect trials) might be interpreted as reflecting an easier and faster switching of attention. However, this result is easily interpretable: go and nogo trials, requiring a higher load of cognitive control, led to a less availability of executive resources for switching the attention toward the next stimulus. Nevertheless, the ERP differences between detect and nogo trials were less clearly expressed, probability because of the overlap of another

negative component, more related to response inhibition, which increased the amplitude of the RON in nogo trials.

Summarizing, electrophysiological and behavioural data converged in revealing that age-related cognitive decline might be, at least partially, attributable to a general slowing of information processes. On the other hand, executive control, if conceptualized as a unitary construct, could not account for the age-related differences evidenced in ICT. This was coherent with the review by Verhaegen (2011), who showed that the reduction on processing speed explained for cognitive deficits in elderly better than the deterioration in executive control. On the other hand, a subprocess of executive control, namely attentional switching, resulted particularly sensitive to age, and it could be a potential candidate to mediate age-related cognitive alterations. Finally, several ERP patterns (i.e., right frontal negativity, the enhanced N2) might be interpreted as reflecting compensatory mechanisms engaged in aging. Taken together, these results clearly highlighted how cognitive aging is a complex and fascinating puzzle, difficultly reducible to a single explanatory mechanism. Moreover it gave support to a more recent theory, the so called scaffolding theory of aging and cognition (STAC; Park & Reuter-Lorenz, 2009), which provided an integrative view of cognitive aging, postulating that behavioural performance in elderly should be understood not only in terms of neuro-cognitive declines but also of compensatory processes.

PART II:

Cognitive and Electroencephalographic Markers of Minimal Hepatic Encephalopathy

CHAPTER 4

MINIMAL HEPATIC ENCEPHALOPATY

4.1 HEPATIC ENCEPHALOPATHY

In the present thesis, I focused on studying Hepatic Encephalopathy (HE), as an example, or model, of pathological aging.

HE reflects a wide spectrum of neuropsychiatric and neuromuscular abnormalities observed in patients with liver cirrhosis, a chronic disease characterized by replacement of liver tissue by fibrosis, scar tissue and regenerative nodules (Ferenci et al., 2002). It is reported that approximately 60–80% of cirrhotic patients display a from of HE of different extent in the course of the disease (Schomerus & Schreiegg, 1993). Although cirrhotic patients do not die because of HE, HE represents a prognostic sign. A recent study (Bustamante et al., 1999) evidenced that the probability of survival after the first episode of overt HE in patients with liver dysfunction is up to 42% at one follow-up year, and 23% at 3 years. HE is a potentially reversible condition, but may also be progressive, and is characterized by alterations in several cognitive functions, behaviour, and personality, as well as in neurological and electroencephalographic patterns (Weissenborn, 1998).

The onset of neuropsychiatric symptoms is usually insidious, characterized by alterations in some aspects of personality and in sleep patterns. Motor symptoms are common, and include lack of movement coordination, asterixis (i.e., tremor of the wrist when the wrist is extended), rigidity and ataxia. In some cases, HE can progress through lethargy to stupor and coma (Butterworth, 2000).

A taxonomy to classify the different forms of HE took into account the duration and progress of HE, and distinguished between three types of HE (Ferenci et al., 2002):

- *Episodic HE*. It is the most common clinical picture and is characterized by overt disturbances of consciousness and changes in cognition. It arises over a brief period of

time and shows fluctuations in severity. It is also distinguished into HE episodes with (precipitated) or without precipitating factors (spontaneous). Precipitating factors can be: uremia, gastrointestinal hemorrhage, dietary indiscretion, use of psychoactive medication or of diuretics that increase renal ammonia release, constipation, dehydration, hypo- or hyperkalemia, and hyponatriemia. Furthermore, the term "Recurrent Encephalopathy" indicates when 2 episodes of episodic HE occur within 1 year.

- *Persistent HE.* This seems to be associated with several cognitive deficits that impair both social and occupational functioning. It also encompasses persistent non-cognitive alterations, such as extrapyramidal abnormalities or sleep disturbances. It is applied to a small group of patients with cirrhosis who display rather constant and clinically overt neuropsychiatric disturbance. It is also subdivided into mild and severe HE, according to the degree of reduction of autonomy. A treatment-dependent persistent HE comprises a subgroup of patients whose symptoms occur after discontinuing medication.

- *Minimal HE (MHE).* It refers to a cognitive/cerebral dysfunction not detectable by standard clinical assessments, but rather by means of neuropsychological or neurophysiological tools. This concept is discussed in greater detail below (Paragraph 4.2).

4.1.1 Pathogenesis and aetiology of HE

Given that HE is often a reversible condition, it seems to be the results of metabolic rather than structural brain alterations. The responsible process seems to be the inefficient hepatic clearance of gut-derived neurotoxins, due to hepato-cellular failure and/or portal-systemic shunting, which in turn leads to alterations in cerebral neurotransmission (Figure 4.1). Indeed, the impaired detoxifying action of cirrhotic liver allows several neurotoxins to reach the brain. Among these, ammonia is the most important (Monfort, Muñoz, El Ayadi, Kosenko, & Felipo, 2002; Sorensen & Keiding, 2007). Ammonia is produced in the gut both by metabolism of nitrogenous substances operated by colonic bacteria and by deamination of glutamine. In healthy individuals, ammonia is metabolised to urea by the liver. In patients with cirrhosis, there is a dysfunction in the enzyme activities that catalyze the urea cycle, and this would cause remarkable alterations in the ammonia detoxification pathway and, in turn, increased ammonia levels in blood (Lizardi-cervera, Almeda, Guevara, & Uribe, 2003; for a review). The kidneys, excreting urea, also contribute to increase the production of ammonia in cirrhotic patients, particularly in conditions of

significant dehydration and gastro-intestinal bleeding. High levels of ammonia are buffered, at least in some extent, by the skeletal muscles, which employ ammonia for the conversion of glutamate to glutamine. This also explains why two conditions such as malnutrition and muscle wasting contribute to hyperammonaemia and enhance the probability of encephalopathy in cirrhotic patients (Tarter et al., 1997). Ammonia easily crosses the blood-brain barrier by diffusion in its neutral form or *via* a transporter in its protonated form (Butterworth, 1996). Increased levels of cerebral ammonia affect the glutamine-glutamate interaction between neurons and astrocytes and are clearly implied in astrocyte swelling as observed in several patients with cirrhosis who die in coma (Butterworth, 2000; Lockwood, Yap, Rhoades & Wong, 1991).

Recently, it has been suggested that inflammatory processes might also play a crucial role in the pathogenesis of hepatic encephalopathy (Arias, Aller, Sánchez-Patan, & Arias, 2006; Shawcross, & Jalan, 2005). Indeed, infection, which typically determines inflammatory phenomena, has been often shown as a precipitating factor for HE (Sherlock, Summerskill, White, & Phear, 1954). It was also reported that healthy individuals, particularly when older, may manifest cognitive alterations during infective episodes (Gleckman, 1992). Finally, markers of systemic inflammatory phenomena have been related to the presence of neuropsychological decline in patients having acute liver failure. Therefore, it has been suggested that the inflammatory responses may enhance the permeability of the blood-brain barrier, and this would increase in turn the deleterious effects of ammonia or other neurotoxins (Arias et al., 2006; Jalan, & Bernuau, 2007).

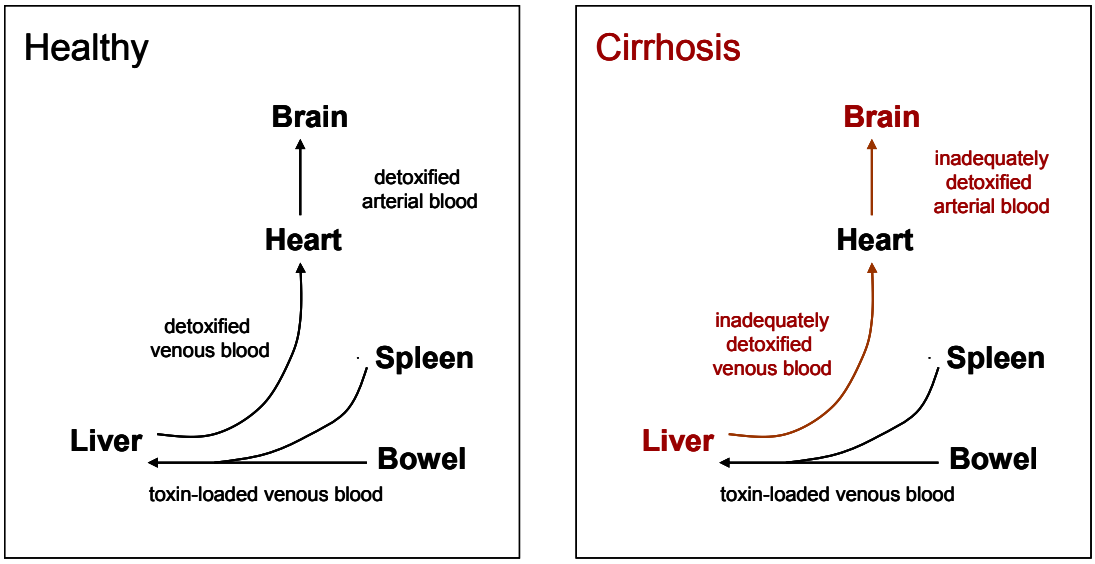

Figure 4.1. Schematic representation of pathogenesis of hepatic encephalopathy. In healthy individuals (**left panel**), neurotoxins produced from bowel are metabolised by the liver, detoxified venous blood returns back to the heart and detoxified arterial blood reach the brain. In patients with cirrhosis (**right panel**), hepatic detoxification is altered due to hepato-cellular failure and/or portal-systemic shunting, hence neurotoxins can reach the brain.

A nomenclature of HE has been formulated according to its aetiology (Ferenci et al., 2002). Three main categories of HE have been proposed: A (acute liver failure), B (porto-systemic bypass without intrinsic liver disease) and C (cirrhosis). Type A encephalopathy classifies the encephalopathy occurring in acute liver failure, which is a rapid deterioration in liver function in patients without pre-existing cirrhosis. Type B is associated with portal-systemic bypass and no intrinsic hepatocellular disease. Portal-systemic bypass (or shunt) is a bypass of the liver by the body's circulatory system and can be either a congenital or an acquired condition. Finally, type C is associated with cirrhosis (Ferenci et al., 2002). In general, the most common cause of HE is cirrhosis, a liver disease characterized by fibrosis and conversion of normal liver architecture into structurally abnormal nodules. Cirrhosis is typically due to excessive alcohol use and viral hepatitis (B, C, D types).

It is worthy of note that clinical manifestations of HE largely depend on the extent, as well as the type, of the liver alteration, and the rate at which liver dysfunction occurs. As an example, the symptoms of HE in patients with acute liver failure (i.e., A type) are very different from those evidenced in patients with cirrhosis (i.e., C type). HE in cirrhotic patients encompasses sleep alterations and attention deficits and develops into disturbed consciousness, disorientation and coma over time periods ranging from days up to months. On the other hand, patients with acute liver failure show modifications in the behaviour

even before the first diagnosed signs of liver dysfunction. In contrast to cirrhotic patients with HE, patients with acute liver failure are often described as irritable and restless. Finally, acute HE may develop within hours to a profound alteration of consciousness (Weissenborn, Bokemeyer, Krause, Ennen, & Ahl, 2005).

4.1.2 Neuropsychological characterization of HE

Clinically, HE clusters a wide spectrum of cognitive and motor disorders (Ferenci et al., 2002; Weissenborn, 1998). The changes in consciousness and mental status vary from slightly and subtle cognitive alterations to severe coma and are graded according to the West Haven criteria (Table 4.1) (Conn et al., 1977; Ferenci et al., 2002). Based on this classification, four different stages of HE are identified, and range from stage 0 comprising patients with both normal cognitive function and minimal HE, to stage 4 that classifies comatose patients.

Stage	Distinguishing Features
0	No abnormality detected
	Trivial lack of awareness
I	Euphoria or anxiety
	Shortened attention span
	Impairment of addition or subtraction
	Lethargy or apathy
II	Disorientation for time
	Obvious personality change
	Inappropriate behavior
	Somnolence to semi-stupor
	Responsive to stimuli
III	Confused
	Gross disorientation
	Bizarre behavior
IV	Coma, unable to test mental state

Table 4.1 West Haven Criteria for the diagnosis of HE. (adapted from Bajaj, Wade, & Sanyal, 2009).

This clinical scale is obviously unsatisfactory. Indeed, stage 0 clusters both normal individuals and patients with MHE. Furthermore, there is a need for sensitive, as well as specific and universally applicable, tools for the assessment of neuropsychiatric condition in patients with cirrhosis. The symptoms of hepatic encephalopathy (HE) may at first

involve deficits in attention, personality changes (as in the case of MHE), lack of attention, psychomotor slowing and extrapyramidal symptoms, such as hypomimia and bradykinesia (in stage-I HE). In later stages of HE, the symptoms may be represented by disorientation and bizarre behaviour, “lack of restraint, nocturnal ramblings, and a peculiar tendency to evacuate bladder and bowels in inappropriate places” (Sherlock et al., 1954) (stage-II HE), and they may end in stupor and coma (stages III and IV).

These neuropsychiatric alterations can be clustered into 4 categories, including changes in consciousness, personality, intellect and speech (Sherlock & Dooley, 2002; Weissenborn, Heidenreich, Ennen, Rückert, & Hecker, 2001b; Weissenborn et al., 2005):

- Disturbed consciousness. It often manifests as a fixed stare, a reduction in spontaneous movement, apathy, slowness and brevity of response, lethargy and hypersomnia. These can progress to coma, which at first mimes normal sleep but subsequently develop to complete unresponsiveness.
- Personality changes. These can include irritability, childishness and unconcern for family or profession. Patients can manifest these personality changes also between acute liver episodes, suggesting a dysfunction of the frontal lobe activity.
- Intellectual deterioration. This varies from subtle attentional deficits or difficulties to perform highly complex tasks to remarkable confusion. Constructional apraxia can be occasionally reported when asking patients to reproduce designs (e.g., star) or to write a sentence (Figure 4.2).
- Speech abnormalities. It manifests as monotonous voice and slurred slow speech. In the severe case of deep stupor, dysphasia is observed and is typically combined with perseveration.

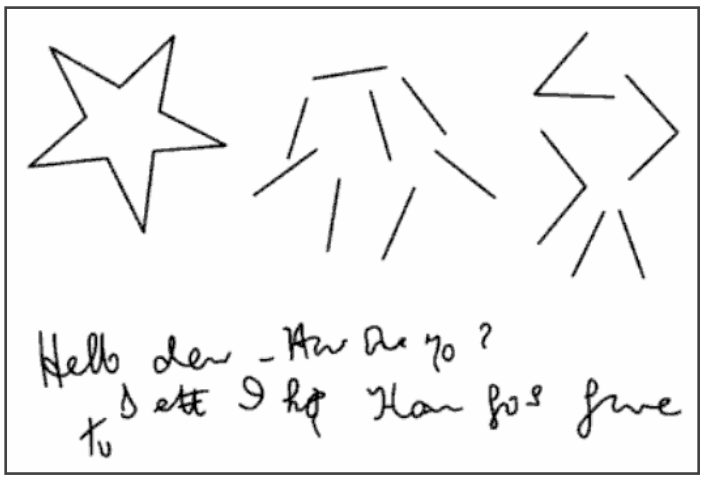

Figure 4.2 Constructional apraxia and writing difficulties in a patient with overt HE, in the absence of visual loss or gross tremor.
- constructional apraxia, observed as inability to copy the drawing of a star;
- writing difficulties: 'Hello dear. How are you? Better I hope. That goes for me too.'
(Adapted from Sherlock & Dooley, 2002).

Regarding the specific cognitive alterations associated with HE, motor symptoms are the most characteristic manifestations of HE, besides both attentional deficits and impairments of visual perception (Weissenborn et al., 2005). Patients with HE may have deficits that resemble even those occurring in neurodegenerative disorders, including Parkinson's disease or multiple system atrophy (Weissenborn & Kolbe, 1998).

Attentional and arousal deficits are also commonly reported (Amodio et al., 2005; Weissenborn et al., 2005). Indeed it has been reported a decline of attention from the first stages of HE, which is often accompanied by a dysfunction of arousal system, over stage II to III, ending in coma. Notably, even patients who appear clinically unaffected (i.e., patients with MHE) show several attentional deficits when tested with adapted psychometric tools.

With regard to memory, there is substantial controversy whether HE affects this function (Weissenborn, Heidenreich, Giewekemeyer, Rückert, & Hecker, 2003). In general, psychometric tests used for the assessment of memory in patients with HE are either oriented toward the knowledge system (i.e., semantic memory) or the working memory. Nevertheless, given that the results in memory tests intrinsically depend also on attention,

there is often no way to clearly know whether the failures observed are attributable to one of these two functions (Weissenborn et al., 2005). However, some tests allowed to better isolate memory function by differentiating between encoding and retrieval phase. Indeed, assuming that retrieval is less influenced by attention than encoding, these tests help to better dissociate memory and attention deficits. A recent study assessed memory functions in 45 cirrhotic patients with stage-0 to stage-I HE comparing them with 52 healthy controls (Weissenborn et al., 2003). Several tests were employed to investigate the short-term memory - such as digit span test, or recurring figures test - and the long-term memory, as the picture memory test (Bäumler, 1974), and the word-figure-memory test (WFMT; Weissenborn et al., 1996). In both the two categories of tasks, patients with early HE had a worse performance respect to controls, indicating that they are impaired in the short-term memory, as well as, in the long-term memory. Nevertheless, it has been impossible to distinguish between difficulties in encoding and retrieval. Some studies used more refined tests such as the Posner test or the Scan test based on the Sternberg paradigm, to disentangle between subtle attention and memory deficit (Amodio et al., 1998a; 1998b). They found impairments on both attention and memory functions, even in those patients who did not show overt HE symptoms (i.e., patients with MHE).

On the other hand, a relatively preserved function in HE is the verbal ability, as shown by several studies (e.g., Gilberstadt et al., 1980; McCrea, Cordoba, Vessey, Blei, & Randolph, 1996).

4.1.3 Neurophysiological characterization and assessment of HE

In clinical practice, neurophysiological assessment of HE relies on electroencephalogram (EEG) and event-related potentials (ERPs). Finally, a psychophysical measure is often utilized for the diagnosis of HE, and is called 'Critical Flicker Frequency' (CFF) index.

EEG. For several reasons (e.g., easy and fast investigation), the EEG is the electrophysiological technique most frequently used to assess and monitor the neuropsychiatric conditions of patients with cirrhosis (Montagnese, Amodio, & Morgan, 2004). The EEG displays a wide spectrum of alterations in patients with HE. However, none of them is specific; thus a diagnosis of HE based uniquely on the neurophysiologic tool is not sufficient.

Nevertheless, the investigation of EEG patterns may be useful for 1) the diagnosis of HE in confuse or comatose patients with severe liver dysfunction, (2) monitoring the staging of HE and the effects of surgical or medical treatments on HE, (3) detecting early stages of HE, such as MHE, and (4) providing prognostic information on the occurrence of overt HE bouts and on survival (Amodio & Gatta, 2005).

Below the main findings about EEG and ERP alterations associated with HE will be described; most of all come from an extensive reviews made by Amodio and Gatta (2005) and by Montagnese and collaborators (2004).

Several EEG patterns are ascribed reflecting HE in confuse or comatose patients and are summarized as follows (e.g., Amodio et al., 1999; Parsons-Smith, Summerskill, Dawson & Sherlock, 1957):

• The low-frequency alpha rhythm (8 Hz) is disturbed by random theta waves over both the hemispheres. Theta waves are usually observed over the temporal areas, but may also be shown over the frontal sites or diffusely over the scalp. Moreover, the lower is the EEG reactivity to eye opening, the severer is the HE.

• Background EEG theta activity is diffused, accompanied by random high delta waves, and occasionally bursts of frontal rhythmic delta activity (FIRDA) or occipital rhythmic delta activity (OIRDA).

• Pronounced disorganization of EEG activity. Diffuse asynchronous waves occur in theta and delta range expressed bilaterally. Triphasic waves, which are synchronous waves with a more anterior expression, appear in trains or runs. They usually have a fronto-occipital lag time, and are superimposed on the slowed EEG rhythm.

• In severe comatose conditions, a decrease of arrhythmic delta activity both in terms of frequency and amplitude may even become a flat EEG.

In order to monitor the progress and to identify the severity of HE, several classifications have been proposed based on different EEG parameters (Parsons-Smith et al., 1957), and obtained by means of both qualitative (Amodio et al., 1999; Rohmer & Kurtz, 1961), as well as semiquantitative (Amodio et al., 1999) methods. The classification based on the semiquantitative method usually concerns the evaluation of the basic posterior EEG activity or the spectral analysis of the EEG signal (Amodio et al., 1999). The evaluation of basic posterior EEG activity was introduced for the first time by Conn and collaborators (1977) and became an integrative part of the index for staging HE, namely the Porto-Systemic Encephalopathy Index, and was later applied in other studies (e.g.,

Amodio et al., 1996; 2001; Bahn et al., 2002; Ciancio et al., 2002; Groeneweg et al., 1998). Specifically, the estimation of the EEG is based on the relative power of frequency bands and the mean dominant frequency (MDF, that is the mean power of each frequency band weighted by the frequency rate) of 100 s of tracing recorded over posterior electrodes (originally, T3-O1, T4-O2) (Figure 4.3). As can be seen in Figure 4.3, the slowing of EEG is manifested as a decrease in band frequency as the severity of HE increases.

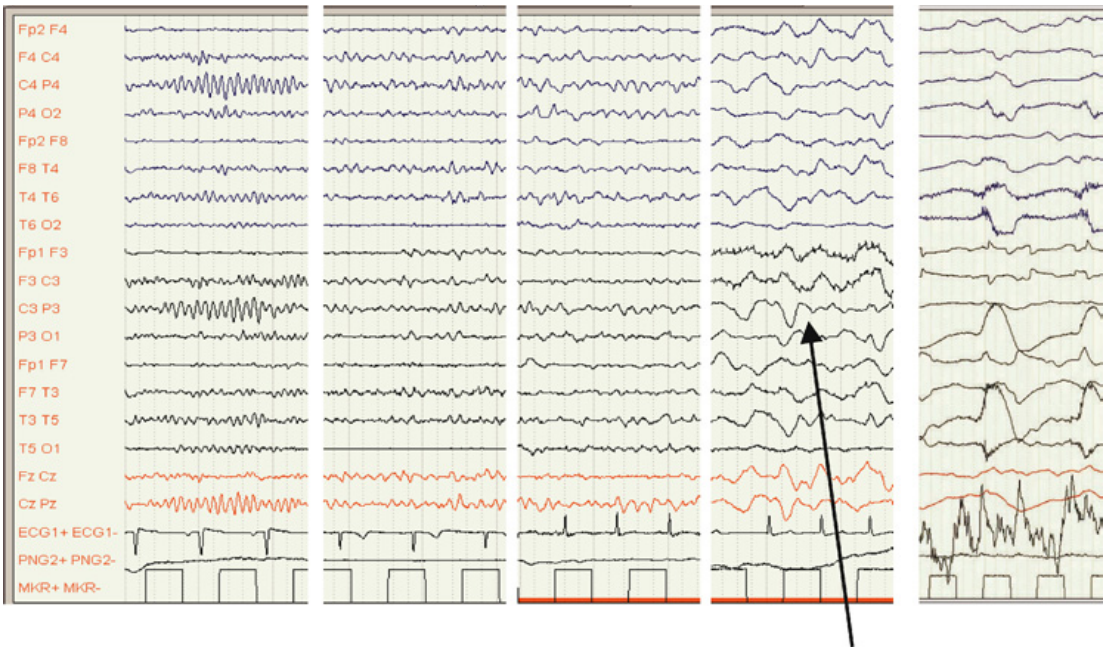

Figure 4.3 Progressive EEG alterations in HE. The figure shows the slowing and the alterations of the EEG in the different stages of HE, as classified by Van der Rijt et al. (1984), and applied in our laboratory. From the left: a normal EEG tracing, alterations stage 1, stage 2, and stage 3. The arrow highlights a triphasic wave. The last panel on the right displays the EEG of a patient in very severe unresponsive coma: the EEG activity is suppressed (figure from our laboratory).

EVOKED POTENTIALS. In addition to the use of EEG, EPs are also useful neurophysiological tools to have a quantification of HE, and to monitor the effects of treatments. A recent review on the EPs alterations in HE was published (Montagnese et al., 2004). Two others were previously published (Chu, Yang, & Liaw, 1997; Kullmann, Hollerbach, Holstege, & Scholmerich, 1995). The EPs are generally categorized as: 1) Exogenous or sensory evoked potentials, elicited by stimulation of auditory, visual or somatosensory systems. 2) Movement-related evoked potentials, associated with the preparation and execution of movements. 3) Endogenous or cognitive evoked potentials,

reflecting cognitive processes (Regan, 1989).

Visual evoked potentials (VEPs). Visual evoked potentials are electrical responses elicited by visual stimulation, such as flashes, pattern-reversal stimuli, or the motion onset in the visual fields. The studies that have investigated VEPs in cirrhotic patients are difficult to compare given their inter-study differences in the populations and in the analysis technique for VEPs. They also led to some inconsistent findings. However, some consistent findings, as highlighted in a recent review (Montagnese et al., 2004), include, for example, the prolongation of several potentials (P1, N2, P2, N3). Interestingly, a reversible delay in N3 seems to occur as the severity of HE increases, and it was found even in 40% of cirrhotic patients who did not show alterations when tested through the classical psychometric and EEG assessments. In the late stages of HE (stage III and IV) it was also shown a reversible loss of N1 and P1 components (e.g., Casellas et al., 1985).

Brainstem auditory evoked potentials (BAEPs). BAEPs are the electrical responses elicited by brainstem structures, such as responses to auditory stimuli (clicks). They are classified in five wavelets, labelled I–V, having amplitudes of 5–15μV and occurring about 50 – 400 ms after the auditory stimulus. There is a notable variation in the findings across the BAEP studies. However, the most common alteration concerns the delay in I, III, IV, and V peak latencies and the I–III and I–V inter-peak latencies; and a positive correlation between latency delay and the degree of HE (Chu &Yang, 1988). Attenuation in BAEPs amplitudes was also reported, but not consistently among the researches.

Somatosensory evoked potentials (SEPs). These potentials originate in cerebral cortex and are elicited by the afferent pathways stimulation from peripheral nerves to the cortex. Several studies reported a prolongation in the peak and inter-peak latencies of the SEPs, which positively correlates with the severity of HE. Notably, such latency prolongation was observed in up to 100% of cirrhotic patients with overt signs of HE (e.g., Yang, Chu & Wu, 1997).

Movement-Related Evoked Potentials. Specifically, the 'Bereitschaftspotential' or Readiness Potential is a slow negative potential starting roughly between 800 and 1000 ms before a voluntary and auto-initiated action and expressed over the motor area contralateral to the movement (Deecke, 2001). Only one study (Kulisevsky et al., 1995) has investigated the alterations of the Readiness Potential occurring in cirrhotic patients who had MHE. The Readiness Potential recorded before the electromyogram onset resulted attenuated in patients, indicating a dysfunction in the activity of the cortical areas implied in movement

preparation (Kulisevsky et al., 1995).

Cognitive Evoked Potentials. The most studied cognitive potential is the P300, which has been commonly elicited by oddball paradigms. There is reasonable consistence across the findings of the P300 studies in cirrhotic patients (e.g., Gallai et al., 1995; Saxena et al., 2002). The findings mainly concern:

• A systematic delay of the P300 latency and, more rarely, an attenuation of P300 amplitude;

• Between 90 up to 100% of patients in the early stages of HE and 20 to 60% of patients with MHE showed a prolongation of P300 latency;

• P300 latency delay correlated with the severity of the HE;

• The delay in P300 latency in patients with MHE (see next paragraphs for more detailed description of MHE) predicted a development of overt HE;

• The P300 amplitude was often shown attenuated in patients with both overt and minimal HE, but less consistently across studies.

CRITICAL FLIKER FREQUENCY (CFF). The CFF refers to as the highest frequency in cycles per second at which a light source can be detected as flickering (Kircheis, Wettstein, Timmermann, Schnitzler, & Haussinger, 2002). At frequencies above the flickering threshold the light source appears as continuous although it is still flickering. CFF is thought to index not only the efficiency of patients' visual pathways, but also of their cerebral cortex. CFF thresholds were observed to be lower in patients with minimal and overt HE than in healthy controls and in cirrhotic patients who were cognitive preserved. The reduction in CFF threshold seems to have a reverse correlation with the severity of the HE. A threshold value was defined as a cut-off to separate the unimpaired and impaired patients. It has been hypothesized that the alterations shown in CFF threshold reflect the presence of a hepatic retinopathy, the severity of which greatly mimics the cerebral alterations observed in these patients (Kircheis et al., 2002).

4.2 MINIMAL HEPATIC ENCEPHALOPATHY

MHE has been described using different names, such as, low-grade, early latent or subclinical HE, to identify cirrhotic patients with subtle cognitive function alterations (Rikkers, Jenko, Rudman, & Freides, 1978). From 20% up to 60% of patients with cirrhosis may manifest MHE, depending on the tests used for its diagnosis and the severity of hepatic failure (Amodio et al., 2004; Dhiman, & Chawla, 2009). The clinical profile of MHE is characterized by cognitive alterations, including changes in selective attention, visuomotor ability, psychomotor speed, response inhibition and selection, and executive functions (e.g., Amodio et al., 1998a; Schomerus, & Hamster, 1998; Weissenborn et al., 2001a; 2001b; 2005). Moreover it involves also electrophysiological abnormalities, detectable by the slowing of the electroencephalogram and/or ERPs alterations (Amodio & Gatta, 2005; Guerit et al., 2009). Therefore, where possible, the diagnosis of MHE is preferably based on a combination of psychometric and neurophysiologic/psychophysiological tools.

In the next sections the neuropsychological and neurophysiological profile of MHE will be described, as well as the batteries and tools used for the diagnosis of MHE.

4.2.1 Neuropsychological profile of MHE

MHE encompasses a variety of cognitive alterations.

Psychomotor slowing has been commonly detected in cirrhotic patients who did not display clinical signs of HE (Elsass, Christensen, Mortensen, & Vilstrup, 1985; Gilberstadt et al., 1980; Schomerus & Hamster, 1998). This slowing does not concern only the motor processes, but also the cognitive ones. The idea of a cognitive, rather than motor, origin is driven by the observation that the delays observed in RTs are smaller in simple RTs tasks respect to choice RTs tasks (Rikkers et al., 1978; Schomerus et al., 1981).

Several attentional processes are altered in MHE (Elsass et al., 1978; Amodio et al., 1995; McCrea et al., 1996; Amodio et al., 1998a; Weissenborn et al., 2001), although some attentional tests failed to show relevant MHE-related deficits (Krieger et al., 1996; McCrea et al., 1996; Tarter et al., 1984).

The literature of MHE usually refers to the classification of attentional processes formulated by Posner and Petersen (1990). These authors hypothesized that attention

consists of vigilance and two other attentional systems: the anterior attention system (AAS), which is implied in response selection, response inhibition and executive control; and the posterior attention system (PAS), which is involved in sustained attention, visual-spatial orienting and focusing of visual attention. The vigilance system has been investigated in some studies (e.g., Weissenborn et al., 2001b) adopting the alertness test, the acoustic and visual tests of vigilance created by Zimmermann and Fimm (1989), and the cancelling d test (Brickenkamp, 1981), which is a test for assessing sustained attention. Performance of patients with MHE in vigilance tests was characterized by an increase in RTs accompanied by a decrease in the number of hits, as compared to that of controls. Also performance in the alertness test resulted impaired in patients with MHE, suggesting a dysfunction in the alertness state. Alterations of sustained attention were confirmed by the cancelling d test. Indeed, the number of items processed by patients was about half of that processed by controls, whereas the number of errors was even more than double (Weissenborn et al., 2001a; 2001b). This pattern of results indicates that patients with MHE might have some abnormalities in the systems mediating vigilance, alertness and sustained attention. In agreement with these findings, some studies showed MHE-related deficits in sustain attention, and interpreted these alterations as responsible of the easy distractibility shown by cirrhotic patients (Amodio et al., 1998a; McCrea et al., 1996).

Taken together, these studies suggest that patients with MHE show deficits with regard to the basic attentional functions (i.e., vigilance and sustained attention).

A classical task to study the function of attention orienting and focusing (PAS system) is the Posner test (Posner & Peterson, 1990). In this task a stimulus appears in one of two squares on the screen. The stimulus could be either peripherally cued by an arrow appearing before the stimulus or not cued. In 80% of the trials the cue appears at the same side as the stimulus. This is the so-called valid condition. In 20% of the cases the cue appears on the opposite side to the stimulus at the invalid position, or no cue occurs. The latter situation is called neutral and a question mark occurs in the middle of the screen. The participants' task is to press a reaction-time button as quickly as possible. Amodio and collaborators (1998a) compared the performance in a Posner task between 100 cirrhotic patients without signs of HE with that of 40 healthy controls. The patients performed worse than the controls in the neutral as well in invalid condition. They also performed worse than the controls in the valid condition; however, the valid cue shortened their RTs as compared to the neutral condition. This pattern of results indicated the reduced ability to

disengage attention once allocated in cirrhotic patients.

Also the functions linked to the AAS are altered in MHE. For example, in a study mentioned above (Weissenborn et al., 2001b), cirrhotic patients were tested in a divided attention task, in a supramodal control task, and in an attention shift task. Again, the patients with MHE performed significantly worse than those without MHE and controls in each of the tasks investigated, both in terms of RTs and number of errors. The impairment of several attentional functions was also shown in a recent study (Felipo et al., 2011), which highlighted how patients with MHE had reduced performance in all the tasks investigated, namely in selective and sustained attention tests and in visuo-motor and bimanual coordination tests.

In a study, Amodio and collaborators (2005) specifically studied the MHE-related alterations in the functions belonging to the AAS versus PAS system. The AAS was investigated by the Stroop task and was measured selective attention and inhibition of irrelevant information. The PAS was studied by means of the Posner task and the Focus task, investigating automatic orienting of attention as well as focusing of attention, respectively. Patients showed an alteration in selective attention and inhibition, as indicated by the altered performance on the Stroop task, but spared functions of attention orienting and focusing. This suggests that the AAS is more vulnerable than the PAS to MHE.

Among the executive functions, the inhibitory control has been object of increasing interest in MHE literature. For example, Schiff and collaborators (2006) utilized a visuospatial compatibility task (Simon task) (Simon & Rudell, 1967), which implies in some trials (i.e., non-corresponding conditions) the activation of a given response and the inhibition of another, more automatic but incorrect, response. Indeed, in the Simone task, two different visual stimuli are presented on either the left or the right side of a computer screen. The task of the participant is to respond as fast as possible to the appearance of the stimuli, by pressing either left- or right-side keys according to the instructions. The “Simon effect” is defined as the slowing of RTs and the reduction of accuracy observed when the position of the target stimulus on the screen does not spatially correspond with the position of the response key (“non-corresponding condition”), on the other hand, if the stimulus and the response correspond spatially, then RTs are faster and accuracy greater (“corresponding condition”). Irrelevant stimulus position produces an automatic activation of the ipsilateral response. The additional time required for inhibiting the tendency to activate the incorrect response in the non-corresponding condition would produce the cost of the Simon effect

(Valle-Inclán, 1996). The study showed a slowing-down of RTs in the non-corresponding condition 58% higher in patients than in controls. Given that the delay was higher in the non-corresponding condition than in corresponding one, it would suggest the existence of a dysfunction involving the control of inhibitory mechanism.

Bajaj and collaborators (Bajaj et al., 2007; 2008a) employed – and suggested to use – a test, called the Inhibitory Control Task (ICT), as a useful tool for the diagnosis of MHE. In the ICT, a continuous stream of letters is presented one after the other. Participants are invited to pay attention only to the letters "X" and "Y," and their task ("go trials") is to press a button every time "X" and "Y" are alternated (called targets), independently of the irrelevant letters presented between them. In contrast, participants must refrain from responding (i.e., to inhibit the response; "no-go trials") when the 2 identical target letters are consecutively presented. Patients with MHE were shown less accurate in inhibiting the response. Moreover, a cut off of 5 lures (i.e., non-inhibited responses) has been claimed to discriminate patients with and without MHE with 88% sensitivity and 77% specificity compared with formal neuropsychological testing (Bajaj et al. 2008a).

On the other hand, other cognitive functions are preserved in patients with MHE. Long- and short-term memories are relatively maintained. Also verbal abilities (Elsass, Lund, & Ranek, 1978; Gilberstadt et al., 1980; McCrea et al., 1996) and concept formation ability (Tarter et al., 1987) are substantially spared in this patients population. Likewise, constructional apraxia is reported only infrequently in patients with MHE (Zeegen et al., 1970).

4.2.2 Neurophysiological profile of MHE

Alterations in the EEG signal and in evoked potentials (EP) are often shown in patients with cirrhosis who have no clinical signs of hepatic encephalopathy.

More specifically, in patients with MHE, the EEG is characterized by fronto-central diffusion of alfa and beta activity (Kullmann et al., 1995), by decreased frequencies in alfa rhythm and a bilateral occurrence of disturbed and unstable random waves in the theta range. Rarely, more severe EEG abnormalities were reported, comprising a diffuse slowing of the EEG activity in the theta range and, more rarely, also the occurrence of random waves in the delta range (Amodio et al., 1999b; Parsons-Smith et al., 1957). Quantitative spectral EEG analysis reported that an increase in the relative power of the delta activity,

and/or a decrease in the mean dominant frequency registered by the posterior electrodes were shown in 15–30% of patients with MHE (e.g., Amodio et al., 1996, 2001; Van der Rijt & Schalm, 1992).

Concerning the alterations in EPs, patients with MHE showed a delay in auditory brainstem potentials (see Paragraph 4.1.4) (Amodio et al., 1997; Mehndiratta, Sood, Sarin, & Gupta, 1990) somatosensory potentials (Kono et al., 1994). Nevertheless, these changes are not specific since they can also be manifested by alcohol abusers (Porjesz & Begleiter, 1981; Virtaniemi, Kuusisto, Karjalainen, Karjalainen, & Laakso, 1995) and by diabetic patients (Virtaniemi et al., 1995).

The P100 component of visual potentials (VEPs) was shown prolonged in patients with MHE in some studies (Weissenborn et al., 1990), but not in others (Sandford & Saul, 1988). In contrast, the P300 was shown delayed in patients with MHE more consistently across studies (Montagnese et al., 2004; Amodio et al., 2004, for reviews). The latency delay concerns both the P3a and P3b components, and was reported in passive as well as active oddball paradigms (Kügler et al., 1994; Saxena, Bhatia, Joshi, Garg, & Tandon, 2001; Weissenborn et al., 1990). Notably, Saxena and collaborators (2001) showed that the P300, when elicited by an active oddball paradigm, may be altered in 20–80% of cirrhotic patients with MHE or with Stage I changes. They also demonstrated, through a follow-up study, that slowing in the P300 latency was able to predict the occurrence of overt hepatic encephalopathy (Saxena et al., 2001).

The P300 amplitude tends to be reduced in patients with MHE (Kramer et al., 2002; Montagnese et al., 2004), although this finding is less consistently shown respect the delay in P300 latency.

Schiff and collaborators (2006) used the ERP analysis in order to examine the efficiency of top-down (i.e., goal-directed) and bottom-up (i.e., stimulus-driven) attentional processes involved during a conflicting task (i.e., Simon task) in a group of patients with MHE. An ERP index of top-down processes is the N2pc, a negative component occurring in the N2 latency-time interval over the posterior sites contralateral to a stimulus position. It also reflects visuo-spatial selective attention (Eimer, 1996). They used the P1 and N1 components as measures of bottom-up perceptual elaboration in the extrastriate cortex. No differences were found between patients with MHE and controls for P1 and N1 amplitude and latency. In contrast, N2pc latency was delayed in these patients as compared to controls. Therefore, this pattern of data suggested that patients with MHE have altered top-

down processes but preserved bottom-up processes.

The same research group (Schiff et al., 2005) investigated the role of inhibitory processes by examining the lateralized readiness potential (LRP) in patients with MHE while performing a Simon task. LRP is a negative potential that precedes voluntary movements and reflects the activation of motor cortex contralateral to the hand that executes the action (Gratton, Coles, Sirevaag, Eriksen, & Donchin, 1988). The LRP resulted delayed in patients with MHE respect controls, especially in the non-corresponding conditions. Such a higher delay in the non-corresponding conditions than in corresponding ones might indicate an impairment of response inhibition processes.

Finally, also the mismatch negativity (MMN) was recently investigated in this patient population (Felipo et al., in press). The MMN is an auditory ERP component elicited when a series of standard sounds is interrupted by deviant and infrequent "oddball" stimuli. The MMN is an index of attentional trigger and reflects the automatic comparison between the ongoing stimulus and its representation stored in memory (Sabri, Liebenthal, Waldron, Medler, Binder, 2006). The MMN area was shown reduced in patients with MHE and was specifically related to impaired performance in attention tasks but not to motor coordination alterations. This idea was driven by follow up analyses, which highlighted that those patients improving in attention tests had a normalization of MMN area. On the other hand, the improvement of motor coordination did not lead to changes of MMN area.

4.2.3 Traditional assessment for the diagnosis of MHE

As mentioned above, an appropriate diagnosis of MHE should be based on both neuropsychological and neurophysiological assessment (Amodio et al., 2004). Here, it will be reviewed the most widely used tools for the diagnosis of MHE.

Paper-Pencil Batteries. The classical batteries used are paper-pencil batteries since they are portable, easily translatable, and with variant forms to prevent learning effects. A recommended battery is the porto-systemic encephalopathy syndrome test or also called Psychometric Hepatic Encephalopathy Score (PHES) (Weissenborn et al., 2001a). It comprises the Digit Symbol Test (DST), the Trail Making Test A (TMT-A), the Trail Making Test B (TMT-B), the Serial Dotting Test (SDT) and the Line Tracing Test (LTT).

The TMT-A tests for psychomotor and selective attention functions, whereas the TMT-B assesses divided attention and executive function. The DST evaluates the speed of

processing, whereas the SDT and the LTT evaluate motor speed and coordination.

Computerized tests. Among the computerized tests, the Inhibitory Control task (ICT) and the Scan task are the most commonly employed.

The ICT (Bajaj et al., 2007) is a modified version of the continuous performance test during which patients are instructed to respond to alternating presentations of two target letters (i.e., X and Y) and to refrain responding to repeating presentations (e.g., an "X" is preceded by an "X" or a "Y" preceded by a "Y"). The ICT assesses a multitude of cognitive processes, including vigilance, sustained attention, working memory updating, and response inhibition. It has been proposed that ICT lures (i.e., numbers of errors in nogo trials) can differentiate between cirrhotic patients with from those without cognitive deficits. ICT performance may also predict the development of overt HE (Bajaj et al., 2007; 2008a).

The Scan test is a digital-recognizing task based on the Sternberg paradigm that measures the RTs and accuracy in recognition of patterns of digits. This is influenced by visual stimulus identification, altered memory scanning, attention, and psychomotor processing defects. Performance on Scan test was also associated with survival (Masini et al., 2003).

EEG. The simple EEG has some value in determining the first or subclinical signs of HE. In the earlier stages of HE, the mean dominant frequency (MDF) of the EEG and spectral analysis are powerful to predict the development of overt HE (Montagnese et al., 2004). Interestingly, the EEG has weak correlations with PHES, probably due to its restriction to examining cortical activity (Amodio et al., 2008).

ERPs. A classical ERP component used for the diagnosis of MHE is P300. Visual P300 was found to be abnormal in 78% as compared with psychometric abnormalities reported only in 41% of cirrhotic patients. However, some inconsistent results might not recommend the use of P300 as a stand-alone measure. Auditory P300 does have good diagnostic potential and can be used, when available, for the evaluation of the neurophysiological profile in cirrhosis (e.g., Montagnese et al., 2004).

CFF. The Critical flicker frequency (CFF) is a test for the functional efficiency of the cortex and has a direct correlation with psychometric alterations (Kircheis et al., 2002). It evaluates the maximum frequency at which a flickering light is still perceived as flickering and not fused. Stepwise increase of the frequency from 25 Hz allows to obtain the fusion-frequency threshold, which is the frequency at which the flickering light is perceived as

fused. Its use has been validated in Europe and India. Nevertheless, CFF was shown not to be so discriminative for the presence/absence of MHE. In the earlier works, it showed a sensitivity of 55% and specificity of 100% in the earlier studies (Kircheis et al., 2002). However, more recent studies underlined an increase in the sensitivity of the CFF (e.g., Sotil, Gottstein, Ayala, Randolph, & Blei, 2009).

4.3 EXPERIMENT 3: TESTING AND IMPROVING THE INHIBITORY CONTROL TASK TO DETECT MINIMAL HEPATIC ENCEPHALOPATHY.

4.3.1 Introduction

As described in detail in previous paragraphs (e.g., Paragraphs 4.2.1-4.2.3), Minimal Hepatic Encephalopathy (MHE) is a milder form of HE detectable by psychometric or neurophysiological testing in cirrhotic patients who appear clinically normal (MHE, Ferenci et al., 2002; Schomerus & Hamster, 1998). It might affect from 20% to 60% of patients with cirrhosis, depending on the tests used for its diagnosis and the severity of hepatic failure (Amodio et al., 2004). MHE impinges on the health-related quality of life (Groeneweg et al., 1998) and it is likely to affect driving ability of these individuals (Bajaj et al., 2008b). It has a negative prognostic value in relation to the occurrence of both bouts of overt hepatic encephalopathy (Amodio et al., 1999) and death (Amodio et al., 2001).

The cognitive profile of MHE is characterized by a peculiar kind of "mild cognitive impairment" regarding selective attention and executive functions, visuomotor ability, psychomotor speed, response inhibition, and response selection (e.g., Amodio et al., 2004 Weissenborn, 1998; Weissenborn et al. 2005). MHE also causes brain dysfunction detectable by the slowing of the EEG (Amodio & Gatta, 2005), prolonged cognitive evoked potentials (Montagnese et al., 2004), and reduced ability to detect light flickering (Kircheis et al., 2002) (see Paragraph 4.2.3 for details on CFF). Therefore, where possible, the diagnosis of MHE is preferably based on a combination of psychometric and neurophysiologic/psychophysiologic tools. Nonetheless, cognitive investigation is the simplest and most widely used way of diagnosing MHE, and the psychometric hepatic encephalopathy score (Weissenborn et al., 2001a), a paper-and- pencil test battery, is one of the preferred tools to this aim (Paragraph 4.2.3). However, its administration requires dedicated, competent personnel, and normative data are available for a limited number of European countries only (e.g., Romero-Gomez et al., 2006; Weissenborn et al., 2001a).

The inhibitory control task (ICT), a computerized psychometric test, has been recently proposed as a simple diagnostic tool for MHE (Bajaj et al., 2007; 2008a). ICT evaluates the ability to inhibit responses during a stressful working memory updating condition. Indeed working memory impairment has been previously shown to be a feature of MHE (Amodio et al., 1998). More specifically in the ICT, a continuous stream of letters is

presented one after the other. Participants are invited to pay attention only to the target letters "X" and "Y," and their task is to press a button every time "X" and "Y" are alternated ("go trials"), independently of the irrelevant letters presented between them. In contrast, participants must refrain from responding (i.e., inhibit the response; "no-go trials") when the two identical target letters are consecutively presented (Garavan et al., 1999).

A cut off of 5 lures (i.e., errors in nogo trials that consist of non-inhibited responses) has been claimed to discriminate patients with/without MHE with 88% sensitivity and 77% specificity compared with formal neuropsychological testing (Bajaj et al., 2008a). Thus, ICT seems to be a promising tool for the diagnosis of MHE. However, its applicability to different populations of patients with cirrhosis and its relation to other measures of MHE need to be confirmed. The aims of the present study were to: *i)* assess the specificity and sensitivity of ICT for the diagnosis of MHE; *ii)* investigate the relationship of ICT measures with other psychometric tests and objective indexes of brain dysfunction useful for the diagnosis of MHE: EEG spectral analysis (Amodio et al., 2002) and CFF (Kircheis et al., 1999); *iii)* evaluate test-retest reliability; *iv)* improve the task if any limitation is evidenced.

4.3.2 Methods

Participants

Seventy-five patients with liver cirrhosis and 55 healthy controls were recruited in two reference centres for the study of hepatic encephalopathy: the Gastroenterology Unit of the University Hospital 'Umberto I' of Rome, Italy (centre A) and the 5th Clinical Medicine Unit of the University Hospital Padua, Italy (centre B).

Participants from centre A were used to assess the specificity/sensibility of ICT for the diagnosis of MHE and to evaluate the test-retest reliability (pooled with normal participants from centre B). The same individuals from centre A were enrolled to validate a model for optimizing ICT interpretation devised in centre B.

Participants from centre B were used for in-deep analysis of both ICT errors and reaction times as well as their relationship with other measures utilized for the diagnosis of MHE, namely EEG spectral analysis (Amodio et al., 2002) and CFF (Kircheis et al., 1999).

They were also used to produce a novel model for interpretation of the ICT outcome results.

Patients with liver cirrhosis from both centres were enrolled consecutively, while healthy controls came from convenience samples of volunteers. The main clinical and demographic features of the study population are presented in Table 4.2. The diagnosis of cirrhosis was based on case history, clinical examination, biochemical, endoscopic, and ultrasound (US) findings, or, when needed, on liver biopsy. The diagnostic criteria were: the presence of hepatic stigmata on routine clinical examination, together with biochemical indices of decompensated liver disease (low serum albumin, high bilirubin, prolonged prothrombin time, low platelet count), endoscopic or US signs of portal hypertension, or a history of previous decompensation (ascites, jaundice, bleeding from esophageal varices). The exclusion criteria were: chronic obstructive lung disease/respiratory failure of other origin, renal insufficiency (creatinine plasma level ≥ 200 μmol/L), coronary heart disease or heart failure of any origin (New York Heart Association –NYHA- lass higher than one), significant neurological/psychiatric disease, overt HE or bouts of over HE within 15 days prior to the study, bleeding or infections within 15 days prior to the study, as well as psychoactive medication (benzodiazepines, antidepressant, neuroleptic drugs), active drinking, or unwillingness/inability to undergo the study procedure. Out of the enrolled patients, 15 in group A and 11 in group B had had previous bouts of overt HE, according to West Haven criteria in the past (>15 days before the study).

The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki and was approved by the local Ethical and the Research Committees.

Psychometric assessment

All patients underwent the Psychometric Hepatic Encephalopathy Score (PHES) that is obtained by a battery of psychometric tests aimed at the diagnosis of HE (see Paragraph 4.2.3 for details), it consists of: the Trail Making Test part-A (TMT- A), the Trail Making Test part B (TMT-B), the Digit Symbol Test (DST), the Serial Dotting Test (SDT) and the Line Tracing Test (LTT) (Schomerus & Hamster, 1998; Weissenborn et al., 2001). Each test was scored against age and education adjusted norms (Amodio et al., 2008). The PHES is the sum of the integer scores of each test computed from the adjusted Z values as follows: score = -3 for $Z \leq -3$, score = -2 for $-3 < Z \leq -2$, score = -1 for $-2 < Z \leq -1$, score = 0 for $-1 < Z < 1$, score = 1 for $Z \geq 1$. In our standardization, PHES is altered if its value ≤ -4

(Amodio et al., 2008). The ICT was administered immediately after the PHES. Two software tools for ICT assessment were used, both kindly provided by Dr. Jasmohan Bajaj who proposed ICT for the diagnosis of MHE (Bajaj et al., 2008a). The task was the same used in the experiment for investigating the electrophysiological correlates of age-related cognitive changes of inhibition ability (for the description of the task, see the Methods section of Experiment 2, described in Chapter 3). Nevertheless, since the tool used in the centre A did not provide the measures about the performance on detect trials (instead analyzed in Experiment 2), this study focused on the performance only in go and no-go trials (but not in detect trials). Specifically, centre A evaluated performance accuracy considering both failures to respond to go trials and failures to inhibit responses to nogo trials (which were called ***lures***), that were omission and commission errors, respectively.

The software tool adopted in center B also allowed us to record RTs, since it worked into an ad hoc experimental software (E-Prime Science Plus Group, Gröningen, The Netherlands), so that all the measures provided by preceding publications could be reproduced (Bajaj et al., 2008a). The psychometric evaluation and the ICT were performed in a quiet room without distracting noises.

Test-retest reliability

A subgroup of 33 controls and 36 patients from centre A agreed to undergo ICT for a second time within seven days after the first evaluation, to assess test-retest reliability. None of the patients experienced changes in neuropsychiatric status, developed other complications of cirrhosis or underwent significant modifications of their treatment regime in between repeat tests.

CFF measurement

In centre B, patients underwent CFF measurement in a quiet, semi-darkened room without distracting noises. A portable, battery-powered analyzer was used (Hepatonorm Analyzer; R&R Medi Business Freiburg GmbH, Freiburg, Germany). The analyzer evokes an intrafoveal light stimulus with defined pulses of light at a wavelength of 650 nm, luminance of 270 cd/m^2, and luminous intensity of 5.3 mcd. The frequency of the red light, which is initially generated as a high-frequency pulse (60 Hz) and which gives the patient the impression of a steady light, was reduced gradually until the patient had the impression that the steady light had changed to a flicker. The patient registers this change by pressing

a hand-held switch. After a practice run, the test was repeated five times and an average value obtained; this was qualified as abnormal if <39 Hz (Kircheis et al, 2002).

EEG assessment

In centre B, patients underwent recording of spontaneous, awake, eye-closed EEG activity by digital EEG equipment (Brainquick 3200, Micromed, Italy) in the morning, generally after breakfast. A standard 21-channel cup (Micromed, Italy) was used and the electrodes placed according to the 10±20 International System. The ground was placed on Fpz, the reference on Oz. Impedance was kept under 5 kΩ. Each channel had its own analogue-to-digital converter (ADC), and signals were digitally filtered in the range of 0.33±60 Hz. The sampling frequency was 256 Hz, the conversion resolution was 0.19 mV/digit. Attention was paid to avoid somnolence and artifacts. After a visual inspection to exclude artifacts, the EEG tracing was assessed by spectral analysis based on Fast Fourier Transform. This was carried out on the derivation P3-P4 in the frequency range of 1±25.5 Hz (Amodio et al., 1999; 2001). The variables considered for EEG evaluation were the mean dominant frequency (MDF, an estimate of the background frequency of the EEG) and the relative amount of slow EEG activity within the delta and theta frequency bands (Ferenci et al., 2002; Amodio et al., 1999).

Statistical analysis

Results are presented as "mean ± SD". Comparisons among the groups were performed by Student's t-test for unpaired or paired data, as appropriate. The correlations between variables were analyzed by means of Pearson correlation or Spearman's rank correlation, as appropriate. The sensitivity and specificity of ICT lures and ICT accuracy in go trials were calculated by the receiving operative curves (ROC).

The Number Cruncher Statistical System (NCSS) software and the 'Statistica 7.1' (Stat Soft Italia srl, 2005) software programs were used.

4.3.3 Results

ICT: comparison between patients with cirrhosis and controls

ICT go accuracy was lower in patients with cirrhosis compared to controls in both the centre A ($t(90)=3.32$; $p<0.01$) and centre B ($t(36)=2.63$; $p<0.05$); while ICT lures (i.e., number of errors in nogo trials) were significantly higher in centre A ($t(90)=-4.83$; $p<0.001$), but not in centre B ($t(36)=-1.3$; $p>0.05$) (Table 4.2). RTs to both go trials and failed nogo trials (i.e., lures) did not significantly differ between patients with cirrhosis and controls (Table 4.2) (all ps. n.s.).

	Centre A (Rome)		**Centre B (Padua)**	
	Controls (n=41)	Patients with cirrhosis (n=51)	Controls (n=14)	Patients with cirrhosis (n=24)
Age (years)	38 ± 15	59 ± 14*	45±16	51±12
Gender (Males %)	41	65	64	71
Education (years)	14.6 ± 3.6	8.5 ± 3.9*	15.4±3.3	10.5±4.3*
Aetiology of cirrhosis (virus/alcohol/other)%	-	66/20/14	-	55/40/5
Child Pugh Class (A/B/C)%		33/47/20		21/57/22
Correct responses (%) in the '*go trials* 'Go accuracy'	0.96±0.03	0.88±0.17*	0.97±0.11	0.83±0.18*
RTs in ICT GO trials	-	-	573±81	632±135
Errors in the '*no-go trials' (lures)* Responses to nogo trials (out of 40)	12.9 ± 5.8	23.2 ± 12.8*	8.5±5.2	11.7±8.1
RTs for ICT lures	-	-	636±161	657±145

Table 4.2: **Demographic variables and ICT measures in controls and patients with cirrhosis in study centres A and B**. Note: * $p<0.05$ patients with cirrhosis vs. controls.

ICT: comparison between patients with and without abnormal PHES

In center A, 20 patients had normal PHES performance while the remaining 31 had abnormal PHES (i.e., the acknowledged criterion for the psychometrical diagnosis of MHE; Randolph et al., 2009). Patients with abnormal PHES had lower go accuracy compared to those with normal PHES (0.83±0.20 vs. 0.96±0.03; $t(49)=3.27$; $p<0.01$). In

contrast, lures were comparable between the two groups (25.2±12.5 vs. 21.4±13.9; t(49)=0.99; p>0.05).

ICT: test-retest reliability

Patients with cirrhosis showed a reduction of the number of lures in the second evaluation compared to the first (17.5 ± 11 vs. 23.3 ± 13.5; t(35)=2.48; p<0.05), but not of go accuracy (0.87 ± 0.15 vs. 0.89 ± 0.15; t(35)=0.49; p>0.05). In contrast, control participants did not show any relevant change either in the number of lures (11.5 ± 7 vs. 13 ± 5.6; t(32)=-1.33; p > 0.05) or go accuracy (0.97 ± 0.06 vs. 0.96 ± 0.03; t(32)=0.77; p> 0.05).

		GO RTs	RTs of lure responses	GO accuracy	Number of lures	Weighted lure responses
Psychometric measures	TMT-A	-0.20	-0.23	0.48§	-0.12	-0,25
	TMT-B	-0.23	-0.35	0.69§	-0.42§	-0,58§
	SDT	-0.22	-0.28	0.55§	-0.25	-0,41§
	SD	-0.11	-0.11	0.51§	0.051	-0,20
	LTT	-0.33	-0.09	0.19	-0.21	-0,17
	PHES	-0.31	-0.24	0.57§	-0.16	-0,01
Spectral EEG measures	MDF	-0.18	-0.11	0.34	-0.20	-0,31
	Delta %	0.02	0.04	-0.37	0.15	0,26
	Theta %	0.30	0.62§	-0.19	0.45§	0,35
	Alpha %	-0.30	-0.56§	0.09	-0.32	-0,17
	Beta %	-0.03	0.10	0.25	0.03	-0,12
CFF		-0.16	-0.21	0.09	0.18	0,13

Table 4.3 Matrix of correlations between ICT outcome measures and other measures of brain dysfunction (paper-and-pencil psychometric tests, EEG and CFF) in patients with cirrhosis from centre B. Note: § = p<0.05.

ICT: insight into the task

In centre B, a U shaped relationship between go accuracy and number of lures were shown in patients with cirrhosis (Figure 4.4). Therefore, in individuals who were unable to reach about 0.85 - 0.90 go accuracy, the information provided by lures was found to be substantially meaningless (i.e., if the participant develops insufficient sustained attention to

respond to go trials accurately, his/her inhibition ability can paradoxically appear elevated). This was further supported by the absence of a relationship between lures and the PHES (R=-0.16 p=0.42), the EEG mean dominant frequency (R=- 0.20 p=0.37), or the CFF (R=0.18 p=0.35). The importance of the accuracy in go trials for ICT interpretation was also supported by the relationship of go accuracy with PHES and its component tests (Table 4.3). Only RTs of lures were found to be related to another measure of brain function: the relative power of theta activity of the EEG (Table 4.3).

The above results made it obvious that adequate interpretation of the lures had to take into account accuracy in go trials. Therefore, a new variable adjusting lures by go accuracy (weighted lures: WL) was calculated as follows:

$$\mathbf{WL= L/(GA)^2}$$

where

WL: weighted lure
L: number of lures (failed inhibition of response; i.e. commission errors in nogo trials)
GA: go accuracy

WL was found to be related to some of the PHES tests, taken as stand-alone variables (Table 4.3). WL proved to be more useful than lure responses in discriminating controls from the patients with cirrhosis with/without MHE resulting from extensive investigation (altered PHES, spectral EEG or CFF) (Figure 4.5). Go accuracy was the only other ICT measure that proved good correlation with cognitive performance, as performance in TMT-A, TMT-B, and was a discriminating value (see Table 4.3). On visual analysis, W-LR=24 and go accuracy=0.75 appeared to be reasonable cut-off values.

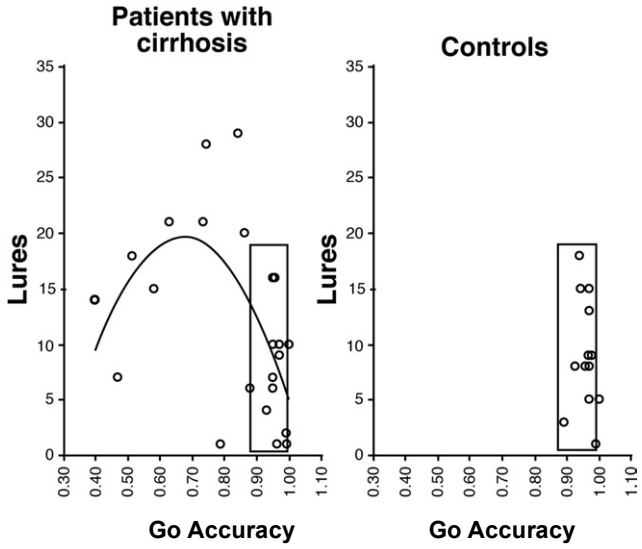

Figure 4.4 Plot of go accuracy and number of lures in the patients with cirrhosis and controls (center B). In a subgroup of patients with cirrhosis (outside the rectangle), ICT performance is different from that of controls (inside the rectangle). A reversed U-shape relationship (panel on the left) was detected between lures and go accuracy in patients with cirrhosis. If go accuracy was low, the estimation of lures is meaningless. Note: the curve is computed by mean square technique with negative exponentials.

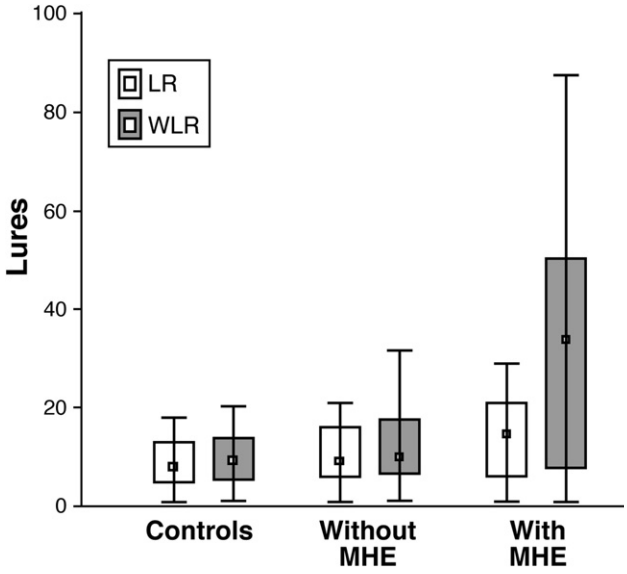

Figure 4.5 Lures and weighted lures (WL) in controls and patients with cirrhosis without and with MHE (abnormal PHES, EEG, or CFF; center B). Note: Small box, median; large box, 25th–75th percentile; bar, minimum-maximal interval without outliers

Testing the model in an independent sample

The model devised in centre B was applied to patients and controls from centre A. ROC curves were calculated for ICT go accuracy, lure responses and WL (Figure 4.6). WL provided a sensitivity/specificity profile, which was better than that of lures, but not superior to that of go accuracy in discriminating patients with cirrhosis with/without PHES alteration (Figure 4.6). The best discriminating values estimated on the basis of the ROC curves are reported in Table 4.4.

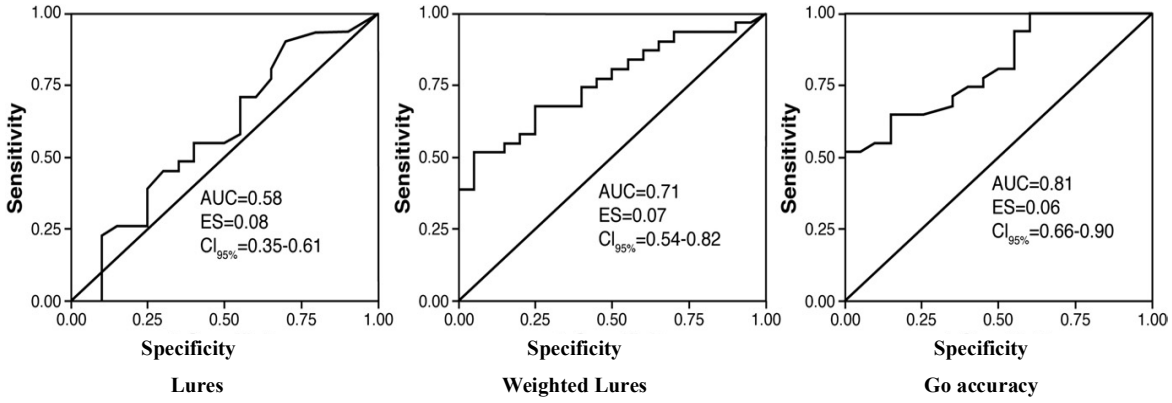

Figure 4.6 ROC curves for lures (left), weighted lures WL (middle), and go accuracy (right). Sensitivity and specificity are calculated in relation to the presence of PHES alteration. Note: AUC, area under the curve.

	Controls (%)	Patients with cirrhosis (%)	
		PHES normal[a]	PHES abnormal
W-LR > 24	3.6	40	74
W-LR > 28	0	40	74
Go accuracy < 0.75	0	0	25
Go accuracy < 0.90	3.6	0	48

Table 4.4 Prevalence of Individuals With Abnormal Weighted Lures and Go Accuracy at Different Thresholds Obtained From ROC Curve Analysis. NOTE: The thresholds were selected by visual inspection. [a]PHES is the acknowledged psychometrical tool for the diagnosis of MHE; therefore, PHES normal = no MHE, and PHES abnormal = MHE.

4.3.4 Discussion

In the present study the number of errors in nogo trials (i.e., lures), which is a measure of the *inhibition ability,* was shown to depend on accuracy in go trials, which reflects the ability in *working memory updating*. Accordingly, the number of lures, as a stand-alone variable, was found not to be adequate for discriminating controls from patients with liver cirrhosis who had PHES alteration. In contrast, ICT go accuracy, as a stand alone, and lures weighted by go accuracy, a newly devised measurement method, were shown to have a better discriminating value, even if the concordance with PHES was found to be limited.

The detection of MHE is a relevant health issue, due to its impact on quality of life and driving ability (Bajaj et al., 2008b). Among the psychometric tools to diagnose MHE by mere cognitive investigation, PHES is considered to be the preferable one, at least in the countries where this battery is standardized (Randolph et al., 2009). However, the use of classical psychometrical batteries, such as PHES, in a clinical setting may be problematic in countries where psychometric tests can only be administered by qualified personnel. For this reason, the use of a computerized test directed towards the study of the cognitive domains that are impaired from the onset of HE is interesting. Computerized tests are generally based on the repetition of a great number of trials, therefore, if the instructions are well understood, the results produced are reasonably more precise than those of paper and pencil tests. The ICT (Bajaj et al., 2007; 2008a), together with the Scan test (Amodio et al., 1998; 1999) are the only computerized tests that have been expressly applied to patients with cirrhosis based on known cognitive features of MHE.

In this study the ICT was performed in two reference centers for the investigation of HE using two comparable software tools. The tool adopted in centre B works within a specific framework for accurate neuropsychological investigation (E-Prime, Science Plus Group, Gröningen, The Netherlands) that ensures complete control of all the experimental conditions. Moreover, in centre B the ICT, as well as other cognitive investigation methods, were performed by expert neuropsychologists, while in centre A the tests were performed by clinicians. Despite these differences, the ICT measures were comparable in the two centres. This finding provides evidence of good accuracy of the ICT measurements in our study.

The finding that ICT measurements showed a relationship mainly with TMT-B, but no relationship with LTT is easily explained by the fact that both ICT and TMT-B reflect executive control functions (e.g., updating in working memory, and attentional switching),

whereas LTT reflects motor functions. This can also explain the lack of relationship with CFF, which is a psychophysical measurement. The relationship of number of errors and RTs in nogo trials (lures) with EEG dynamics seems to highlight that lures have an objective relationship with brain dysfunction, even if the relationship between ICT and neurophysiologic dynamics requires further ad hoc investigation (see Experiment 4, next paragraph).

However, the results did not fit completely with the report originally published by Bajaj and collaborators (Bajaj et al., 2008a), whose controls had quicker reaction times to both go and lures than ours (490±62 vs. 573±81 ms. and 535±81 vs. 636±161 ms., respectively), as well as lower number of lures (3±2 vs. 12±6). In contrast, go accuracy was comparable (0.96±0.6 vs. 0.96±0.04). Neither age nor education can explain the difference between the Italian and the USA controls, since they were comparable. A possible explanation for this unexpected finding is that USA controls might have been more familiar with computer use and games. This hypothesis is also supported by the fact that a trend for a lower attitude in performing the ICT test in Italian people compared to the USA people is also supported by the same worse ICT performance in the Italian patients with cirrhosis compared with the USA patients. This finding indicates the need for standardization of the ICT in different populations.

The detection of a reversed U shaped relationship between go accuracy (working memory updating) and lures (inhibition) suggests that testing inhibition in the context of insufficient attention and working memory abilities produces unreliable results. Indeed, a low accuracy in go trials indicates that many trials had a missing response (in go trial an error is a missed response). But if a participant commits a lot of missing responses, he/she is more likely to "perform" correctly on nogo trials (hence to not respond when actually it is required to not respond). However the low number of error in nogo trials is a spurious effect. This phenomenon can explain why lures did not differ between patients with/without PHES abnormalities and consequently justify their poor ROC curve profile. Thus, a new variable (lures weighted by go accuracy) was codified, adjusting the number of lures based on go accuracy. The newly devised variable WL proved to be useful. WL allows us to evaluate inhibition ability based on each individual's working memory ability. The value of WL measurement was supported by a ROC curve profile that was clearly better than that of lures. However, even WL did not prove to be better than go accuracy, as a simple measure of working memory updating. This is in agreement with previous studies

(Amodio, 1999; McCrea et al., 1996; Weissenborn et al., 2005) proving that selective attention and working memory tasks are very good psychometric tools to detect MHE.

Additional finding obtained from this study was a trend for a learning effect, at least in the patients with cirrhosis. The absence of learning effect in control participants can be explained by the ceiling effect, since normal participants with normal performance might simply not be in a position to improve their high performance any further.

A limitation of this study was the small but significant higher education and lower age of controls compared to patients with cirrhosis. However, since these variations could have only improved ICT performance in controls, its diagnostic power might have been, if anything, slightly overestimated, which would not affect the study conclusion. In conclusion, the present study proves that: 1) the ICT provides cognitive measures that are related, albeit only roughly, to recommended diagnostic standards for cognitive investigation of MHE, 2) the ICT, as most psychometric tools exhibits some practice effect, 3) the value of the ICT outcome lures (*inhibition ability*) becomes more valuable if it is adjusted by go accuracy (*working memory ability*), 4) testing for *working memory* and *attention* is as important as testing for *inhibition* to diagnose cognitive dysfunction in patients with cirrhosis.

4.4 EXPERIMENT 4: ELECTROPHYSIOLOGICAL ALTERATIONS IN MINIMAL HEPATIC ENCEPHALOPATHY EXAMINED USING THE ICT.

4.4.1 Introduction

The Inhibitory Control Task (ICT) has been proposed as a useful test for the diagnosis of minimal hepatic encephalopathy (MHE) (Bajaj et al., 2008a). It is an adapted version of the paradigm used by Garavan and collaborators (1999) and provides information about several cognitive functions, starting from the low-level abilities (i.e., sustained and selective attention), to the high-level ones, such as working memory updating and response inhibition. In the previous experiment (Experiment 3) we assessed the efficacy of ICT, and we found that performance on go trials was able to discriminate patients with MHE from controls, whereas performance in nogo trials did not have an adequate discriminative value. This was due to the fact that, when the attention and working memory abilities were insufficient, the measure of inhibition ability became meaningless. Indeed, if a participant committed a lot of missing responses (because of working memory and/or attention impairment), he/she was more likely to "perform" correctly on nogo trials (hence to not respond when it was actually required to not respond).

However, the behavioural ICT measures alone are not able to clearly establish which cognitive functions are particularly affected in MHE. Indeed, it is possible that the inhibitory processes are impaired in MHE as well, but the performance in nogo trials is not a reliable measure of inhibition efficacy (unless considered together with go accuracy). Moreover, performance in go trials does not only imply a working memory updating process, but is also mediated by more basic functions, including sustained and selective attention. Thus, there is no way to attribute if patients' impairment on go trials performance was due to deficits on working memory or attention abilities, or both.

The present experiment tried to overcome these limitations. Firstly, it considered also the performance in a baseline block, in which participants were required to respond whenever the target letters X and Y were presented (called detect trials), regardless of their sequence of occurrence. In this way, detect trials provided a purer measure of attention, without the concurrent influence of working memory processes. Secondly, and more importantly, it took advantage of the excellent temporal resolution of event-related

potentials (ERPs) to investigate possible abnormalities related to MHE on each specific process involved in ICT task. In this regard ICT was a suitable task to have an overview of MHE-related cognitive alterations, since it assessed a plurality of processes, including attention, working memory updating and inhibition.

In order to evaluate the attentional processes, the P3a and reorienting negativity (RON) components were examined. The P3b and nogo-P3 were used as indices of working memory updating and response inhibition, respectively. Finally, N2 was examined since it provides a measure of controlled top-down resources allocated whenever a stimulus needs to be processed and a response selected (Folstein & Van Petten, 2008; Luck & Hillyard, 1994).

Considering in more detail each ERP component, the P3a (a subcomponent of the P300) is a positive wave occurring roughly 300 ms post-stimulus and showing a fronto-central distribution (Friedman & Simpson, 1994; Polich, 2007). The P3a is believed to index the process of attentional capture, and is probably related to the identification of an infrequent stimulus (for a review, see Escera, Alho, Schröger, & Winkler, 2000).

The RON components are late negativities, can have a frontal or parietal distribution, and appear after P3 waves (Berti, 2008a; Schröger & Wolff, 1998a). They have been proposed to reflect the reorientation of the attentional focus (e.g., Berti & Schröger, 2001; Escera et al., 2001; Munka & Berti, 2006). Importantly, both the P3a and RON components seem to reflect the activation of attentional switching, which is a fundamental step of orienting of attention (Escera et al., 2000; Friedman, Cycowicz, & Gaeta, 2001).

The P3b is the other subcomponent of the P300, and represents the ERP correlate of information updating in working memory (Donchin & Coles, 1988; Kok, 2001; Polich, 2003; 2007). The P3b is a positive component reaching its maximum amplitude over the parietal regions of the scalp. The peak latency of P3b occurs approximately 300 to 400 ms post-stimulus and is thought to reflect classification speed, which is proportional to the time needed to evaluate a target stimulus (Kutas, McCarthy, & Donchin, 1977; Magliero, Bashore, Coles, & Donchin, 1984).

The nogo-P3 is a positive deflection over central sites, peaking between 300 and 600 ms post-stimulus, and is related to response inhibition processes (Falkenstein, Hoormann, & Hohnsbein, 1999; Kok et al., 2004; Pfefferbaum, Ford, Weller, & Kopel, 1985; Ramautar et al., 2004).

The N2 is an early negativity developing between 150 – 400 ms post-stimulus. It is not

a unique component, but encompasses a series of negativities elicited by different paradigms (e.g., mismatch negativity or MMN, N2pc, N2c) (Folstein & Van Petten, 2008; Näätänen et al., 2001). Thus, the N2 has been interpreted as reflecting different processes, including conflict monitoring (e.g., Donkers & Van Boxtel, 2004; Nieuwenhuis, Yeung, Van den Wildenberg, & Ridderinkhof, 2003), inhibition (e.g., Falkenstein et al., 1999; Kok et al., 2004), and attentional processes (Luck & Hillyard, 1994). However, there is some consensus in considering the N2 as an index of cognitive control, as reviewed in a recent study (Folstein & Van Petten, 2008).

In the investigation of electrophysiological changes related to MHE, the majority of the studies focused on the P300. Almost all these studies did not dissociate between P3a and P3b components (see Montagnese et al., 2004, for a review), hence the cognitive correlates indexed by the specific P300 components have been poorly explored in this patient population. In general, P300 was consistently found delayed in patients with MHE (Kügler et al., 1994; Saxena, Bhatia, Joshi, Garg, & Tandon, 2001; Weissenborn et al., 1990) and this prolongation of the P300 latency was shown to predict the occurrence of overt HE (Saxena et al., 2001). In contrast, findings regarding the P300 amplitude are less coherent, and they generally reported a reduction of P300 amplitude in patients and MHE (Montagnese et al. 2004).

Two components belonging to the N2 family have been recently examined: the N2pc, a negative component occurring over the posterior sites contralateral to a stimulus position (Schiff et al., 2006), and the MMN, an auditory ERP negativity elicited when a series of standard sounds is interrupted by deviant and infrequent “oddball” stimuli, (Felipo et al., in press). Both the N2pc and MMN resulted altered in patients with MHE. These findings led to the suggestion that patients with MHE have difficulties in several attentional processes, such as the selection of relevant information (Schiff et al., 2006) and the comparison between the stimulus and its representation in memory (Felipo et al., in press), respectively.

To our knowledge, neither the RON nor the nogo-P3 has been ever investigated with respect to hepatic encephalopathy in general and, more specifically, in the case of MHE.

Given the ERP findings on MHE described above (for a more detailed description, see Paragraph 4.2.2), it seems clear how far we are from understanding the specific cognitive and neural markers of MHE. Therefore the present study was aimed at simultaneously investigating different cognitive processes, and their electrophysiological counterparts, in

cirrhotic patients with and without MHE. This was made possible by examining the performance and the ERPs in three ICT conditions that vary depending on the type of process required: 1) detect trials, requiring mainly sustained and selective attention, 2) go trials, which also imply a process of working memory updating, and 3) nogo trials, which require response inhibition. We hypothesized that MHE-related deficits in a given cognitive process (e.g., in attentional processes) would be reflected in an alteration in the latency and/or amplitude of its ERP correlate (e.g., P3a).

Importantly, we anticipated that several ERP components were found unexpectedly increased (rather than decreased) in cirrhotic patients without MHE as compared to healthy controls. This might indicate the recruitment of compensatory mechanisms in patients who did not reveal any sign of brain dysfunction (even when assessed with the sophisticated psychometric and EEG tools). These findings are noteworthy since they suggest the need to open a debate about the definition of the boundary between the presence and the absence of MHE.

4.4.2 Methods

Participants

Forty-eight participants were enrolled in the study: 31 patients with liver cirrhosis (age 54 ± 10 years, mean ± S.D.; 25 males; education level: 11 ± 4 years), and 17 age-matched healthy controls (age 54 ± 13 years; 7 males, education level 15 ± 2 years). None of the participants had uncorrectable impairment of visual acuity, neurological or neuropsychiatric disorders, and significant cardiovascular, respiratory or renal impairment. None of the patients took psychotropic medication. The diagnosis of cirrhosis was made on the basis of historical, clinical, laboratory, endoscopic and radiological findings. None of the patients had evidence of overt hepatic encephalopathy at the time of the present study.

Minimal hepatic encephalopathy (MHE) was diagnosed based on spectral EEG features (Amodio et al., 1999; 2001) and performance on validated paper and pencil psychometric tests, including TMT-A, TMT-B, Digit symbol test, serial dotting test (SDT) and line tracing test (LTT), to obtain the psychometric hepatic encephalopathy score (PHES, Amodio et al., 1998; Amodio et al., 2007; Weissenborn et al., 2001). Patients were considered to have MHE if at least one measure (psychometric tests and/or EEG) was

abnormal (Ferenci et al., 2001). Based on these criteria, 13 patients were qualified as having MHE, and 18 without MHE. Also control participants underwent the same battery of psychometric tests. Informed consent was obtained from all participants.

	Controls	**Patients with MHE**	**Patients without MHE**
Number	17	13	18
Age (years)	54 ± 13	54 ± 5	53 ± 11
Education (years)	15 ± 2	9 ± 3	13 ± 4
Aetiology of cirrhosis virus/alcohol/mixed (n)	-	3/6/4	9/6/3

Table 4.5. Demographic variables of the sample

Stimuli and Procedure

All participants were required to perform the ICT. Stimuli, task and procedure were the same of those employed in Experiment 2 (for the description of stimuli and procedure, see the Methods section of Experiment 2, described in Chapter 3 of the present thesis). EEG was recorded simultaneously to the ICT performance.

Behavioural analysis

The percentage of accuracy was obtained for detect, go and nogo trials and was analysed through a 3 × 3 ANOVA with trial type (detect vs. go vs. nogo trial) as the within-subjects factor and group (controls vs. patients with MHE vs. patients without MHE) as the between-subjects factor.

To assess response speed, RTs in detect and go trials were analysed by means of a 2 × 3 ANOVA with trial type as the within subjects factor and group as the between subjects factor. When required, post-hoc analyses were run with Newman-Keuls correction. Partial eta-square (η^2) values were calculated for all ANOVAs as an effect size index.

Electrophysiological recording and pre-processing

EEG signal was recorded and analysed in the same way of that employed in the experiment concerning age-related changes in ICT (for the details about EEG recording and ERP pre-processing, see the Methods section of Experiment 2). After the procedure of epoch rejection and the exclusion of the epochs containing an error, the final averaged ERPs were based on a mean of 86 % (range 68% - 94%) relative to the original number of epochs.

ERPs analysis

The analyses were focused on those ERP components that were commonly shown reflecting the investigated processes (i.e., attention, inhibition, working memory updating). Therefore, peak latency and peak amplitude were obtained for N2, P3a, P3b, RON and nogo-P3.

The choice of the derivations for the ERP analyses was driven by the literature concerning the scalp distribution of these ERPs, by visual inspection of the main differences between patients with cirrhosis and control participants, and by the findings obtained from Partial Least Square Analysis (see below).

The analyses of latency and amplitude of the ERP peaks were carried out by means of 3 × 3 × 3 ANOVAs with derivation and trial type (detect vs. go vs. nogo trials) as within subjects factors and group (patients with MHE, patients without MHE and controls) as between subjects factor. Peak latency and amplitude of the N2 were measured over centro-parietal derivations (3 levels of the "derivation" variable: CP1, CP2 and CPz) in the time-window of 100-450 ms post-stimulus. P3a was calculated over frontrocentral derivations (3 levels of the derivation variable: FC1, FC2 and FCz) in the 300-700 ms time-window. Concerning the P3b, the levels of the derivation factor were P3, P4 and Pz and the time-window was 300-800 ms. The parietal RON was calculated on the same derivations (P3, P4, Pz) at 600-1100 ms time-window. Finally, the nogo-P3 was calculated in the 400-900 ms time-window, over central derivations (C3, C4, Cz).

Post-hoc contrasts were performed to explore the significant effects evidenced by ANOVAs. When sphericity was violated (i.e., when the Mauchley sphericity test was significant), the Huynh and Feldt correction (1976) was applied. Partial eta-square (η^2) values were calculated for all ANOVAs as an effect size index.

Partial Least Square analysis

Partial Least Square (PLS) analysis was carried out in order to explore the ERP alterations related to MHE across the different trial types. For the description of PLS analysis, see the Method section of Experiment 2 (Chapter 3).

The PLS analysis included nine task conditions obtained by crossing the 3 trial type (detect, go and nogo trials) × 3 group (patients with MHE, patients without MHE and control participants) levels. The latent variables are considered significant when p is inferior to .05. Bootstrap ratios greater than 2.5 were chosen as the cut-off for stable non-zero saliences.

4.4.3 Results

Behavioural results

The ANOVA on percentage of accuracy revealed a significant main effect of the trial type [$F(2,90)=23.12$; $p< .01$, $\eta^2=.35$], with a lower accuracy for the nogo trials (76± 7%) as compared to both the detect (90 ± 4 %) and go trials (85 ± 10%), all ps<.01. Furthermore, the performance was significantly lower in go than detect trials ($p< .05$). The main effect of group was significant [$F(2,45)=7.40$; $p< .01$, $\eta^2=.26$], with patients with MHE (76 ± 17 %) having a lower percentage of accuracy in the performance as compared to both patients without MHE (86 ± 15%) and control participants (90±9%), regardless of the type of trial considered (all ps<.01). The percentage of accuracy did not significantly differ between patients without MHE and controls ($p>.05$). The interaction between group and trial type was not significant ($p>.05$).

Therefore, the percentage of correct responses was influenced by trial type, being lowest in nogo trials, intermediate in go trials and highest in detect trials, for all the groups. Additionally, patients with MHE performed worse than both controls and patients without MHE, in all types of trials (Figure 4.7).

The analysis of RTs on detect and go trials revealed a significant effect of trial type [$F(1,45)=52.74$; $p< .01$, $\eta^2=.53$]. RTs were slower in go trials (583 ± 73 ms) than in detect trials (537 ± 66 ms). The main effect of group, as well as the group × trial type interaction, were not significant.

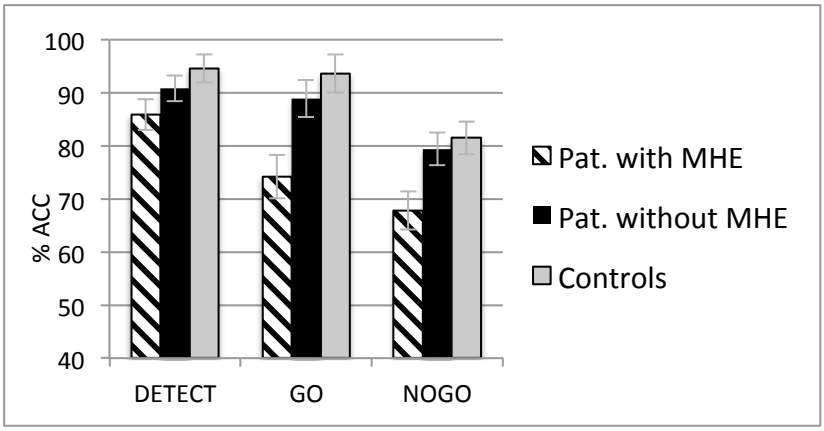

Figure 4.7 Percentage of accuracy for the different trial types (i.e., detect, go and nogo trials) in patients with MHE, without MHE and healthy controls.

ERP results

From a visual inspection, cirrhotic patients, and especially those with MHE, seem to have a reduced P3a over frontal and frontocentral sites, in particular in detect trials. Moreover patients with MHE had a delay of several ERP components, such as P3b and RON components (Figure 4.8).

On the other hand, it is interesting to notice that cirrhotic patients without MHE showed an enhancement of several ERPs, not only relative to patients with MHE, but also to controls. For instance, they displayed a more negative N2 and a more positive nogo-P3 compared to the other groups, over centroparietal and central sites (Figure 4.8). These observations have been confirmed by the following statistical analyses.

P3a

The ANOVA on P3a latency over frontocentral derivations (FC1, FC2, FCz) revealed a significant effect of trial type [$F(2,90)=4.14$; $p< .05$, $\eta^2=.08$], with the P3a being slower in nogo and detect trials as compared to go trials. The main effect of derivation [$F(2,90)=4.69$; $p< .01$, $\eta^2=.08$] was also significant, since the P3a was slower in FC1 than in the other two derivations. The main effect of group and the interaction between trial type and group were not significant ($p> .05$).

Concerning the analysis on peak amplitude, the effects of derivation [$F(2,90)=5.33$; $p< .01$, $\eta^2=.11$], as well as the derivation × trial type interaction [$F(4,180)=12.19$; $p< .05$, $\eta^2=.21$] were significant. Post-hoc analyses revealed that in FC1, P3a was smaller in go

trials, intermediate in detect trials and greater in nogo trials (all ps< .05). The interaction between trial type and group showed a trend toward significance (p = 0.06). Since this lack of significance might be due to a problem of statistical power, a further ANOVA was run with a new variable that merged cirrhotic patients with and without MHE. As expected, in this analysis the trial type × group interaction was significant [$F(2,92)=3.44$; $p< .05$, $\eta^2=.07$]. Post-hoc analyses showed that cirrhotic patients (both with and without MHE) had a less positive P3a compared to controls in detect trials (all ps<.05) whereas no significant differences between cirrhotic patients and controls were found in go and nogo trials (ps > .05).

In summary, the latency of P3a was influenced by the type of trial and by the derivation considered. The P3a amplitude was greater in nogo trials (especially over FC1 derivation). Notably, it was less positive in cirrhotic patients than controls, but only in detect condition (Figure 4.8).

N2

The ANOVA on N2 latency (measured in centroparietal derivations, CP1, CPz, CP2) did not reveal any significant effect (all ps>.05).

The analysis of N2 amplitude revealed the significant effect of group [$F(2,45)=3.35$; $p< .05$, $\eta^2=.13$]. The N2 was significantly more negative in patients without MHE than both in patients with MHE and in control participants (all ps< .01).

Further significant effects were the main effects of trial type [$F(2,90)=11.25$; $p< .01$, $\eta^2=.20$] and derivation [$F(2,90)=28.07$; $p< .01$, $\eta^2=.38$], as well as the trial type × derivation interaction [$F(4,180)=7.78$; $p< .01$, $\eta^2=.15$]. The exploration of such interaction showed that, in CP1 and CPz, N2 was more negative in detect trials than in the other two trial types; whereas in CP2, N2 was more negative in detect trials and in nogo trials than in go trial (all ps< .01).

Summarizing, N2 amplitude was more negative in cirrhotic patients without MHE compared as in the other two groups, and it was influenced by the type of trial, being in general more negative in detect trials.

P3b

The analysis of P3b latency (measured in parietal derivations, P3, Pz, P4) showed the significant main effects of derivation [$F(2,90)=8.20$; $p< .01$, $\eta^2=.15$], and trial type [$F(2,90)=25.50$; $p< .01$, $\eta^2=.36$], with a delayed P3b in nogo than in go and detects trials (all $ps< .05$).

The interaction between group and derivation [$F(4,90)=2.71$; $p< .05$, $\eta^2=.11$], and the three way trial type × group × derivation interaction [$F(8,180)=2.19$; $p< .05$, $\eta^2=.09$] were significant. Indeed in detect trials, P3b was significantly delayed in patients with MHE compared to controls (in Pz) and also compared to patients without MHE in P4 (all ps <.05).

The analysis of P3b amplitude revealed only the significant effect of derivation [$F(2,90)=4.02$; $p< .05$, $\eta^2=.08$], with P3b greater over Pz than over P3 and P4 (all $ps< .05$).

In summary, the P3b latency in detect trials was delayed in patients with MHE respect the other groups, especially over right and middle parietal regions.

RON

The latency of parietal RON component (analysed over P3, Pz, P4) was significantly influenced by derivation [$F(2,90)=4.15$; $p< .05$, $\eta^2=.08$] and group [$F(2,45)=3.92$; $p< .05$, $\eta^2=.15$] factors. Specifically, cirrhotic patients, both with and without MHE, showed a delay of parietal RON components compared to controls (all ps <.01).

Concerning the analysis on amplitude of P3b, the main effects of trial type [$F(2,90)=14.47$; $p< .01$, $\eta^2=.24$], derivation [$F(2,90)=9.18$; $p< .01$, $\eta^2=.17$], as well as the trial type × derivation interaction [$F(4,180)=6.64$; $p< .01$, $\eta^2=.13$] were significant. The investigation of the interaction revealed that the RON component was more negative in detect trials than in go and nogo trials, over P3 and Pz derivations (all $ps< .01$).

In summary, a delay in the parietal RON latency was shown in cirrhotic patients respect to controls (Figure 4.8). Moreover, the amplitude of this component was influenced by the type of trial with detect trials having the most pronounced RON.

Nogo-P3

The analysis of nogo-P3 latency (in central derivations, C3, Cz, C4) showed the significant effects of trial type [$F(2,90)=22.05$; $p< .01$, $\eta^2=.33$] and the interaction between trial type and derivation [$F(4,180)=2.50$; $p< .05$, $\eta^2=.05$]. Post-hoc analyses showed that nogo-P3 was slower in nogo trials than in detect trials, in all the derivations considered, and it was also delayed in nogo than in go trials in C4 and Cz (all ps <.01).

Concerning the amplitude of nogo-P3, the main effects of trial type [$F(2,90)=13.70$; $p< .01$, $\eta^2=.23$] and derivation [$F(2,90)=6.83$; $p< .01$, $\eta^2=.13$] were significant. Additionally, the trial type × group interaction was also significant [$F(4,90)=3.08$; $p< .01$, $\eta^2=.13$]. This means that in nogo trials, patients without MHE had a more positive nogo-P3 as compared to both patients with MHE and control participants (all ps< .05, Figure 4.8). Finally, the trial type × derivation interaction was significant [$F(4,180)=5.02$; $p< .01$, $\eta^2=.10$], with the nogo-P3 being greater in nogo than in go trials (in Cz) and greater in nogo than go and detect trials, in C3 (all ps< .01). Furthermore in these two derivations, it was significantly higher in detect respect than in go trials (all ps< .01).

In summary, the nogo-P3 amplitude was increased for patients without MHE than for the other two groups, in nogo trials. Both latency and amplitude were affected by the type of trials. Indeed, nogo-P3 was greater and delayed in nogo trials, especially in the left and middle central regions.

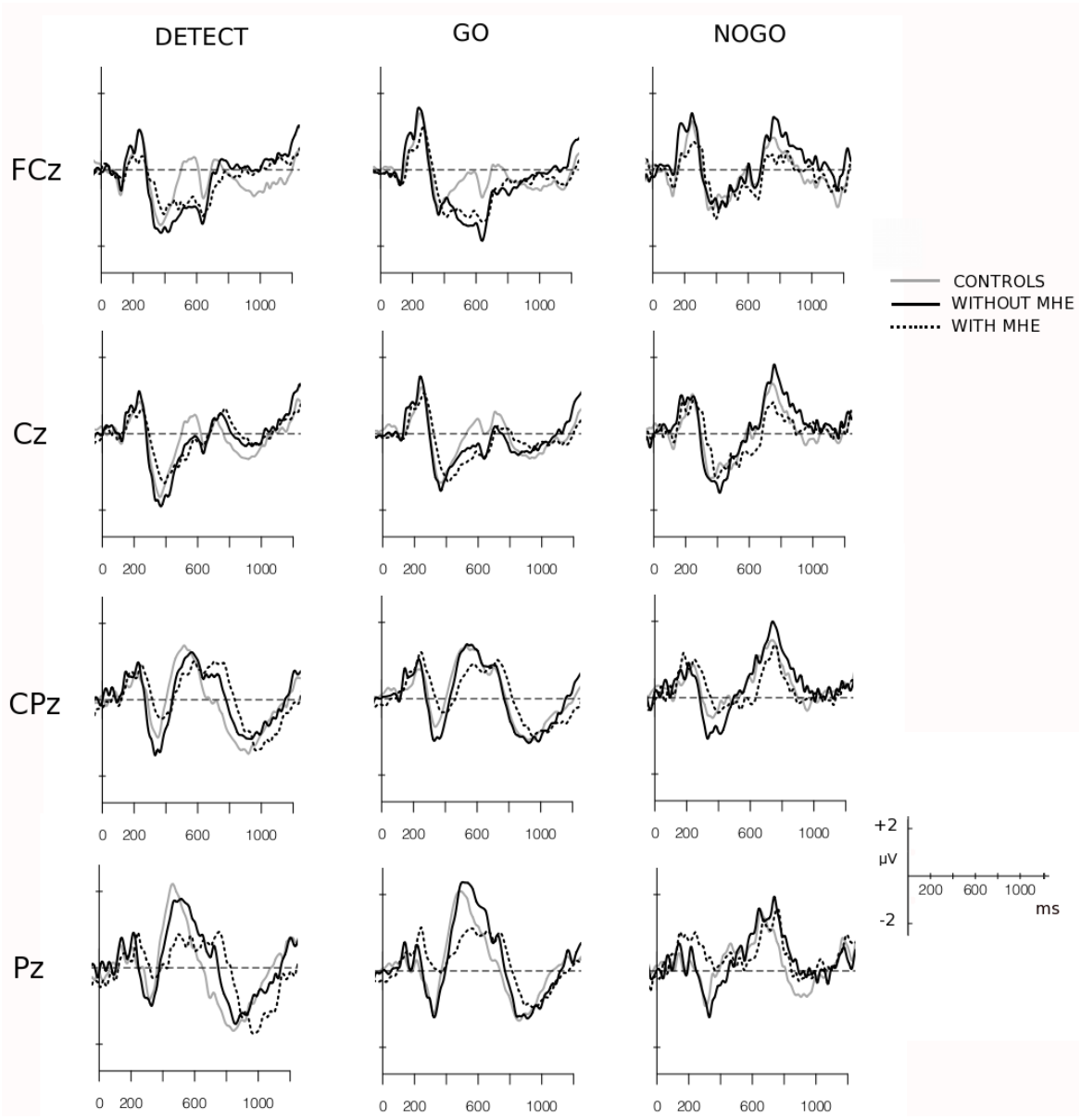

Figure 4.8 Grand average ERP waveforms in patients with MHE, without MHE and controls in midline derivations. The plots show the ERPs of controls (gray line), patients without MHE (black continuous line) and patients with MHE (black dashed line) of the Cz and Pz derivations), separately for detect, go and nogo trials. Since no remarkable between-hemisphere differences in MHE effects were found, only midline derivations are reported here.

Results from PLS Analysis

The PLS analysis allowed to better clarify the main ERP alterations associated with MHE. The permutation test revealed two significant latent variables.

The first LV ($p < .0001$), which accounted for 64.13% of the crossblock covariance matrix distinguished nogo trials from detect and go trials, in all the three groups (Figure 4.9). Nevertheless, as can be seen in the figure of the brain scores (Figure 4.9), the contrast between nogo trials and the other two trial types was more expressed in controls and in patients without MHE, and less in patients with MHE. The electrodes salience reflected an enhanced and delayed positivity over parietal (P3, Pz, P4), centro-parietal (e.g., CP1, CPz, CP2), central (C3, Cz, C4) and frontocentral regions (FC1, FCz, FC2), which indicated the nogo-P3. Furthermore, it was clear the anteriorisation of the P3 component (that is the nogo-P3), which became more pronounced over central and frontocentral regions respect than the posterior regions. Finally, a late negativity over prefrontal and right frontal regions (Fp2, F8) distinguished nogo trials from the other trial types.

The second LV ($p< .0001$), which accounted for 15.93% of the crossblock covariance matrix distinguished go trials from detect trials, but particularly in controls and in patients without MHE (Figure 4.9). Indeed, it captured a variation in the pattern of brain scores across the groups: brain scores were high for detect trials in controls and in patients without MHE, but not in patients with MHE. The LV2 was expressed over frontal (F3, Fz, F4) and frontocentral (FC1, FCz, FC2) sites as an enhanced P2 in go trials respect than detect trials, and, on the other side, as an enhanced P3a over frontocentral sites in detect respect than in go trials. Over parietal regions (P3, Pz, P4), LV2 reflected an increased positivity (namely the P3b) in go trials (than detect ones). Finally, in the most posterior sites (O1, O2) and lateral parietal sites (P7, P8), this LV expressed a more negative N2 in go, than detect trials.

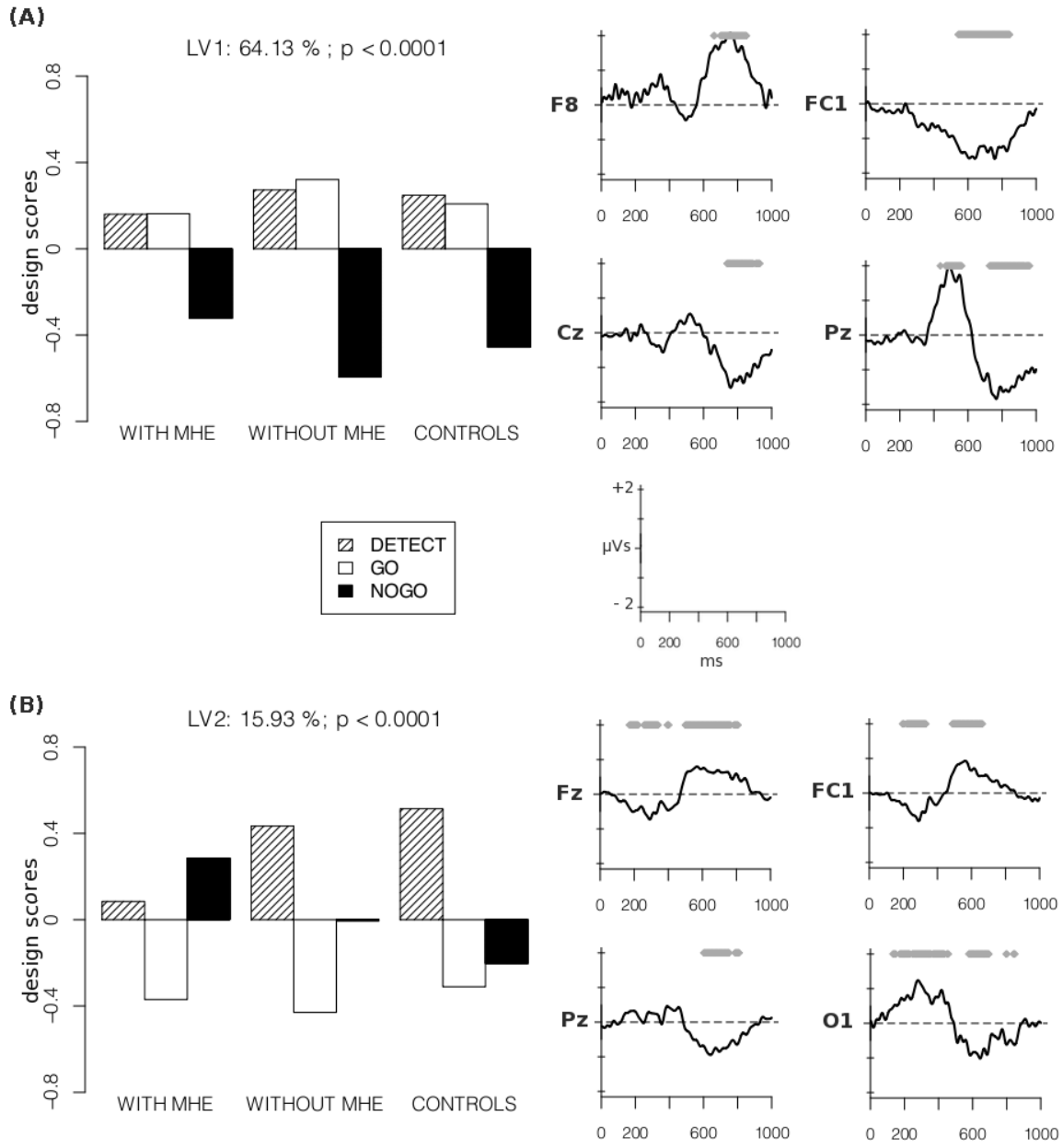

Figure 4.9 Results of the PLS analysis contrasting detect, go, and nogo trials in patients with MHE, without MHE and healthy controls. (A) The first LV reflects the neural correlates of inhibition in all the three groups. (B) The second LV reflects the differences across the three groups, especially with regard to detect trials. Indeed, detect trials (dashed rectangle) were highly expressed in this LV in controls and patients without MHE, but not in patients with MHE.

4.4.4 Discussion

The present study was aimed at investigating the electrophysiological alterations associated with minimal hepatic encephalopathy in different cognitive processes, including basic functions, hence selective attention, and more complex and high-level abilities, such as working memory updating and inhibitory control. To this end, the performance and the ERPs elicited by ICT (Bajaj et al., 2007; 2008a; Amodio et al., 2010) were compared among cirrhotic patients with a diagnosis of MHE, cirrhotic patients without MHE and healthy individuals.

Likewise to the Experiment 3, also this experiment reported a declined ICT performance in patients with MHE respect than the other two groups (i.e., patients without MHE and control participants). This decline was shown occurring not only in nogo trials and go trials, but already in detects trials, leading to the suggestion that cognitive impairment related to MHE does not concern selectively the inhibitory and/or working memory processes, but also more basic abilities, such as selective attention (Amodio et al., 1999; 2005; Weissenborn et al., 2005; Felipo et al., 2011). Two alternatives might be proposed to explain this pattern of cognitive alterations. First, MHE is associated with widespread cognitive deficits that involve multiple domains. Second, the deterioration of low-level abilities, for example selective attention, might affect performance in high-level cognitive tasks since the last one imply such basic functions. In order to disentangle between the two accounts, and explore the neural alterations associated with MHE, the ERPs elicited by ICT were recorded and analysed in the three different types of trials (detect, go, nogo trials).

The main findings from the ERPs analysis can be grouped as 1) evidence of MHE-related alterations mainly in the ERPs elicited by detect trials (than go and nogo trials), 2) enhancement, instead of the expected decrease, in the amplitude of several ERP components in patients without MHE, respect than both patients with MHE and, more interesting, even controls. These two main findings will be discussed below.

The results from the ANOVA analyses showed selective alterations of the ERPs in detect trials, especially in patients with MHE, which consisted of a reduction in the P3a amplitude over frontocentral sites and a delay in the P3b latency. These results are confirmed by the pattern of data described in the designed scores of the LV2 in PLS analysis. Indeed this LV distinguished the ERPs in detect trials - from those in go trials - in controls and in patients without MHE, but not in patients with MHE. Specifically, the

electrode salience of the LV2 revealed that patients with MHE did not show an enhancement of frontocentral P3a in detect trials (respect than in go trials), as instead evidenced in controls and in patients without MHE. These results may indicate that MHE is associated with an impairment of low-level cognitive abilities, such as attention. Indeed, detect trial was the lowest demanding condition of the ICT task (if compared to the other two conditions) and it required to maintain sustained attention to the task, and to selectively respond to target stimuli, ignoring the distracters ones. To respond to the question entered above, it seems reasonable hypothesize that the decline observed in complex tasks (e.g., nogo trials in ICT) was due to a remarkable impairment of low-level, attention mechanisms. This result supported the conclusions of Experiment 3, concerning the appropriateness for a diagnosis of MHE to test for low-level abilities (i.e., attention) before, or together with, testing for high-level abilities (i.e., inhibition) (Amodio et al., 2010). Moreover, it was in agreement with the previous studies, which highlighted deficits in the selective and sustained attention in patients with MHE (Amodio, 1999; Amodio et al., 2005; Felipo et al., in press; McCrea et al., 1996; Weissenborn et al., 2001; Weissenborn et al., 2005). In particular, Amodio and collaborators (2005) suggested that this reduced ability to cope with attentional tasks, requiring both to pay selective attention to target information and to inhibit irrelevant information, was related to an alteration of the Anterior Attention system (AAS; Posner & Petersen, 1990).

Concerning the specific ERP alterations, the prolongation of P3b latency, as observed in our patients with MHE, has been previously documented in several studies, and indicated that patients with MHE have a pronounced slowing-down of stimulus processing (see Montagnese et al., 2004, for an overview of the ERP alterations in cirrhotic patients). On the other hand, it is more interesting the finding of an alteration in the P3a amplitude, given that changes on P300 amplitude were found less consistently in literature (Montagnese et al., 2004). P3a is an index of focal attention mechanisms and working memory, and has been shown to originate from frontal/dopaminergic networks (Polich, 2007; for a review). Thus, a suggestive hypothesis might be that alterations of this ERP component in MHE seems to be the electrophysiological counterpart of a dysfunction in the neural network connecting the prefrontal cortex with the dopaminergic-mediated basal ganglia system (Joebges, Heidemann, Schimke, Hecker, Ennen, & Weissenborn, 2003; Lockwood, Murphy, Donnelly, Mahl, & Perini, 1993; Lockwood et al., 1998). It corroborates the idea that the AAS dysfunction mediates cognitive alterations in MHE, as postulated by Amodio

and collaborators (2005). Indeed the AAS functioning is supported by the activity of the network linking the anterior frontal regions with basal ganglia (Shallice, 1988; Pardo et al., 1990; Stuss, Floden, Alexander, Levine, & Katz, 2001).

A reduction of P3a amplitude in detect trials was shown also in patients without MHE, leading to the suggestion that even cirrhotic patients who did not reveal deficits with the standard diagnostic tools, have ERP alterations. This confirms the claim that, among the cognitive functions, attention is the most sensitive to cirrhosis-related neural dysfunctions (Amodio et al., 2005; Felipo et al., 2011; McCrea et al., 1996; Weissenborn et al., 2001; Weissenborn et al., 2005).

A further result supporting this claim consisted in the prolongation of the RON component, shown both in patients with and without MHE. Indeed, since parietal RON reflects the reorientation of attention (Berti, 2008), a shift in such an ERP component might indicate that cirrhotic patients take longer in reorienting attention to the stimuli of a task, after having been engaged in processing a relevant stimulus (Amodio et al., 1999).

The second main, and quite surprising, finding concerns the enhancement of several ERP components (namely, the N2 and nogo-P3) in cirrhotic patients without MHE. To our knowledge, this is the first evidence of an increase, instead of a decrease, in the ERP amplitudes in cirrhotic patients without MHE (see Montagnese et al., 2004). Such an ERP enhancement seems to reflect a compensatory mechanism to cope to the difficulties of the task.

The investigation of the neural mechanisms required for compensating cognitive deficits has gained an increasing interest in the neuroscience literature, and especially in neurocognitive aging (Cabeza et al., 2002; Daffner et al., 2006; Duarte, Ranganath, Trujillo, Knight, 2006; Stern, 2002). Specifically, in this field of research it was found that, as compared to young subjects, cognitively high performing old individuals, but not low performing ones, generated a larger frontal P3 (e.g., Daffner et al., 2006; Daffner et al., 2011). It appears that high performing old adults compensate for the age-related neural and cognitive alterations by recruiting more attentional and controlled resources (as indexed by the P3) to maintain an acceptable level of performance. In other words, high performing old adults rely upon additional neural activity and additional attentional resources for overcoming the difficulties of the tasks (see Experiment 1, in Chapter 2 of the present thesis for an example of compensatory mechanism). Similarly, in the present study, patients without MHE (i.e., those patients who did not show any alteration, neither on

psychometric battery nor on spectral EEG analysis) revealed a performance comparable to that of control individuals. Nevertheless, from the electrophysiological point of view, they showed an increased no-go P3 in nogo trials respect to the no-go P3 in controls (and patients with MHE). Since the P3 amplitude was shown to be sensitive to the amount of cognitive resources (Daffner et al., 1998; Kok, 2001), such a nogo-P3 enhancement might be interpreted as reflecting the recruitment of additional resources in order to adequately inhibit response and, hence, to have an adequate performance. In a similar way, also N2 was shown more negative in patients without MHE, as respect to controls (and patients with MHE), in all the types of trials considered. The N2 components are a large family of ERPs that seem to be related to different processes, including cognitive control, response inhibition, response conflict (Folstein & Van Petten, 2008). Findings from Experiment 2 (Chapter 3) revealed that ICT trials elicited an N2 that might be an index of executive control. Likewise for the nogo-P3, also the enhancement of N2 in patients without MHE might be a compensatory mechanism, reflecting the allocation of additional executive resources for overcoming difficulties in the task. Therefore, also cirrhotic patients without MHE might also have cognitive deficits, as indicated by the P3a attenuation and the delay of the RON component. However they might overcome such alterations by recruiting additional controlled resources, as evidenced by the increase of N2 and nogo-P3 components.

Thus, it is interesting to notice that not only cirrhotic patients with MHE, but also patients without MHE showed several electrophysiological changes; nevertheless in this latter case, such electrophysiological changes were not only the reflection of a neural dysfunction, but rather, also an index of the engagement of compensatory mechanisms. These last findings are relevant for the conceptualization of the neural condition in those cirrhotic patients who did not reveal any alteration with the standard diagnostic tools. Indeed a question comes into the mind: is it possible that some of the patients without MHE are actually patients with a well-compensated MHE?

4.5 EXPERIMENT 5: THE IIV OF P300 AS AN INDEX FOR DETECTING NEURAL DYSFUNCTIONS IN PATIENTS WITH LIVER CIRRHOSIS

4.5.1 Introduction

The aim of the present experiment was to investigate the intra-individual variability of RTs and P300 parameters in healthy individuals and in cirrhotic patients (with and without MHE). The IIV of RTs has been object of study in a multitude of researches, and has been proposed to be an index of brain dysfunction (Hultsch, MacDonald, Hunter, Levy-Bencheton & Strauss, 2000). On the other hand, the IIV of the ERPs has been poorly investigated (e.g., Fjell & Walhovd, 2007; Fjell, Rosquista, & Walhovd, 2008), probably because of the intrinsic limitations of the methods used for estimating the ERPs (i.e., the average of the sweeps). In the present experiment we used a new method, based on the Bayesian single-trial estimation technique, to obtain a measure of the IIV of the P300 parameters (latency and amplitude) under normal and pathological condition. The extraction of single-trial parameters allowed us to explore the relationship between RTs and P300 parameters, and hence to better understand the functional meaning of P300.

Usually, when reaction times (RTs) are examined, individual performance is described as the mean of several measurements obtained by investigating the participant's performance in a multitude of repeated trials. However, the study of intra-individual variability (IIV) of RTs is now considered an emerging topic in the field of cognitive neuroscience (MacDonald, Nyberg, & Bäckman, 2006). As an example, the evolution of RTs variability along lifespan from childhood to old age is well represented by U-shaped function. Indeed, the IIV in RTs typically decreases from childhood to adulthood and increases in older individuals (Hultsch, MacDonald & Dixon, 2002; Williams, Hultsch, Strauss, Hunter, & Tannock, 2005).

Increased IIV in response speed could be also considered as a marker of brain dysfunction, at least in some patient populations (Hultsch et al., 2000). Specifically, an enhancement of IIV of RTs is detectable: *i*) in dementia (Christensen et al., 2005; Hultsch et al., 2000; Murtha et al., 2002), *ii)* in traumatic brain injury (Burton, Hultsch, Strauss, & Hunter, 2002; Stuss, Murphy, Binns, & Alexander, 2003), *iii*) in attention-deficit hyperactivity disorder (ADHD) (e.g., Castellanos et al., 2005), and *iv*) in schizophrenia (Kaiser et al., 2008).

In a recent study (Bellgrove, Hester, & Garavan, 2004), increased behavioral IIV during

an inhibitory control task was associated with increased brain activity in middle frontal, left precentral and right middle frontal regions. This result suggests that individuals with higher IIV activate inhibition-related brain regions to a greater extent, probably reflecting greater requirements for top-down executive control (Bellgrove et al., 2004). Moreover, Murtha and collaborators (2002) showed that patients with frontal lobe dementia had a higher IIV than patients with Alzheimer's disease, indicating a key role of executive frontal functions impairment in determining increased IIV. Following a new prospective of brain functioning, an incomplete deactivation of the default mode network (i.e., a set of regions consistently more activated during rest periods; Raichle et al. 2001), during task execution was also suggested to be a correlate of increased variability of RTs (Kelly, Uddin, Biswal, Castellanos, & Milham, 2008). Within this framework, it is worthy noting that in individuals with ADHD, a lack of default network suppression was found to be linked to increased distractibility and increased response speed variability (Fassbender et al., 2009).

In general, variability of response speed may depend on perceptual, cognitive, motor or peripheral factors. Unfortunately, the use of behavioural measures as stand-alone is not suitable to highlight the processes that determine the IIV of response speed.

The ERPs might provide information about in which stage of information processing stream the increase of variability occurs. However, when extracted with the averaging technique, the ERPs do not provide information about trial-by-trial associations between brain and behavioral responses.

Recently, single-trial analysis of ERPs was introduced in order to determine the brain activity expressed in each trial during a cognitive task. The single-trial approach seems to be the most appropriate method for proper investigating the relationship between electrical brain activities and IIV in response speed (De Lucia, Michel, & Murray, 2010; Fjell, 2007; Hu, Mouraux, Hu, & Iannetti, 2010).

Indeed, single-trial ERP analysis was shown able to yield newer information about the IIV of P300 in both normal individuals (Fjell, Rosquist, Walhovd, 2009; Saville et al., 2011; Walhovd et al., 2008) and clinical populations (Roth, Roesch-Ely, Bender, Weisbrod, & Kaiser, 2007). More specifically, normal aging was found associated with an increased IIV of both latency and amplitude of P300 responses (e.g., Walhovd & Fjell, 2007; Fjell et al., 2009). Likewise, individuals with schizophrenia showed an enhanced latency and amplitude variability in several ERP components (Roth et al., 2007).

The P300 component seems to be particularly suited for investigating the neural and cognitive locus of RT variability and the relationship between RTs and brain activity (Sutton et al., 1965). The P300 correlate is generally assumed to be a reliable neurophysiological correlate of the stimulus evaluation process (Magliero et al., 1984; Polich, 2007; Rugg & Coles, 1995; Schiff et al., 2008). However, it was recently suggested that P300 is not only related to stimulus evaluation but also to response selection, or at least to some initial decision stages in the stimulus-response association (Verleger, 1997; Verleger, Jaskowski, & Wascher, 2005). In particular, Verleger and collaborators (2005) have argued that P300 reflects a process mediating between perceptual analysis and response initiation, and that consists in monitoring if the decision to classify a given stimulus is appropriately transformed into action.

The investigation of IIV in pathological conditions, such as MHE, helped us in disentangle between these different possibilities. Indeed, an increased variability of RTs in MHE (as observed in previous studies, Elssas et al., 1985; Schiff et al., 2006) without a corresponding increased variability of P300 latency would imply that the variability of stimulus evaluation, or of the early phase of response selection (as supposed by Verleger and collaborators' study), are not affected by MHE; thus the observed increased variability of RTs should be related only to late response processes involved in response execution.

Usually, the standard deviation (SD) of RTs is used to estimate the IIV of reaction time. However, the distributional analysis of RTs provides a more dynamic description of differences in within-subject speed variability between groups and it can yield information on the shape of RT distribution (Balota & Yap, 2011; Castellanos, Sonuga-Barke, Milham, & Tannock, 2006; Ratcliff, 1979). Nevertheless, so far, no study has investigated the relationship between the distribution of reaction times and P300 parameters using a single-trial approach, neither in normal individuals nor in a clinical population.

There are several reasons that suggest the importance of studying the relationship of P300 and RT parameters in MHE. First, two studies (Elssas et al., 1985; Schiff et al., 2006) showed increased IIV of RTs in patients with cirrhosis, especially in patients with MHE. Second, studies adopting the classic oddball paradigm (Amodio et al., 2005b; Klüger, 1996; Saxena et al., 2002) showed that patients with MHE displayed a delayed and attenuated P300 respect controls. Since the reduction of P300 amplitude might be also explained by an increase in the IIV of latency (i.e. grater latency jittering), as evidenced by Mouraux and Iannetti (2008), thus an increased IIV of the single-trial P300 latency is

hypothesised. Finally, likewise to individuals with ADHD, an abnormal activation of the default network was found also in patients with cirrhosis. Indeed the default network of these patients was found not completely suppressed during the execution of an interference task that required the allocation of cognitive resources (Zhang, Yang, Yin, Liu, & Qi, 2007).

Summarizing, the present experiment was designed to investigate 1) whether MHE was associated with increased IIV of P300 parameters; 2) whether P300 amplitude reduction in patients with MHE depends on a reduction of P300 response *per se*, or an increased latency jittering, or both; 3) which relation occurred between behavioural performance and single-trial P300 parameters in healthy and pathological conditions, in order to better identify the functional role of P300.

To accomplish such aims, behavioural and P300 responses were obtained in a stimulus-compatibility conflict task (i.e., the Simon task, Simon & Rudell, 1967; Simon, 2011) in healthy controls and in cirrhotic patients. Concerning the electrophysiological measures, P300 parameters were measured by means of both the classical averaging technique and the Bayesian single-trial P300 estimation technique (D'Avanzo, Schiff, Amodio, & Sparacino, 2011). The IIV of P300 was obtained by calculating the standard deviation (SD) of single-trial P300 parameters. Whereas the SD as well as the distributional analysis of RTs have been taken into account as indices of response speed IIV.

4.5.2. Methods

Participants

A total of 43 participants were enrolled in the study: 29 patients with liver cirrhosis (age: 51 ± 9 years, mean ± SD; males 66%; education level 9 ± 4 years), of whom 14 had MHE and 15 did not have MHE, and 14 age-matched healthy controls (age 49 ± 10 years, males 57%, education 13 ± 5 years).

None of the participants had a history of or current alcohol misuse, neurological or neuropsychiatric disorders, or significant cardiovascular, respiratory or renal impairment. None of the patients had taken psychotropic medication or had an uncorrectable impairment of visual acuity or was colour blind. The diagnosis of cirrhosis was made on the basis of historical, clinical, laboratory, endoscopic and radiological findings. The

aetiology of cirrhosis, the Child-Pugh classification of hepatic insufficiency and the laboratory variables are reported in Table 4.6. None of the patients had evidence of overt hepatic encephalopathy at the time of the present study.

Clinical characteristics		
Aetiology (%)	HBV	24.1
	HCV	48.3
	Alcohol	3.5
	Other	24.1
Child-Pugh classification (%)	A	16.7
	B	55.6
	C	27.8
Biochemical variables	**median (SE)**	
Total Bilirubin (mmol/L)	48.4 (6.9)	
Albumin (g/L)	46.6 (14.6)	
Protrombin Time [PT] (%)	60.6 (3.6)	
Venous ammonia (mmol/L)	59.7 (13.5)	
Na (mmol/L)	139.4 (0.6)	
Urea (mmol/L)	6.7 (8.9)	
Creatinine (mmol/L)	87.6 (4.4)	
Glucose (mmol/L)	17.8 (8.1)	

Table 4.6 Clinical characteristics of patients with cirrhosis.

Detection of MHE

Minimal hepatic encephalopathy (MHE) was diagnosed based on spectral electroencephalographic (EEG) features (Amodio et al., 1999a; 1999b; 2001) and performance in age- and education- adjusted, validated paper and pencil psychometric tests, including the Trial-Making test (TMT part A and B), Symbol-Digit test, and the computerized SCAN test (Amodio et al., 1998, 2008). Patients were considered to have MHE if at least one measure (psychometric tests and/or EEG) was abnormal (Ferenci et al., 2002). On the basis of this criterion, 14 patients were classified as having MHE.

Behavioural task (Simon task)

In the present study, the Simon task, a spatial stimulus-response conflict task, was chosen to obtain behavioural and P300 responses (Simon & Rudell, 1967; Simon, 2011). In the Simon task, participants are asked to respond using spatially arranged keys to a non-spatial stimulus attribute (i.e., colour) of laterally presented targets. The Simon effect refers to the finding that RTs are usually faster and more accurate when the stimulus and response hand positions spatially correspond (notably, the spatial position was irrelevant to the task). This difference in reaction speed and accuracy is explained in terms of competition between a direct route carrying the response linked to the spatial position of the stimulus, and an indirect route holding task demands, at a response selection stage. In the Simon task, P300 amplitude and latency are both sensitive to stimulus-response correspondence: latency is delayed and amplitude reduced in the non-corresponding condition compared to the corresponding condition (Valle-Inclan, 1996; Wascher et al., 1996). Therefore, it was suggested that the Simon task is a cognitive paradigm particularly suited to investigating the relationship between P300, the stimulus-response association and RT parameters (Verleger et al., 2005).

In each trial the participant was presented with a red or a green checkerboard on the right or the left side of the computer screen, whereas a 'neutral' black and white checkerboard always appeared on the other side. The distance between the eyes and the screen was fixed at 80 cm. Participant was told that M key (right side of the keyboard) corresponded to the red checkerboard and Z key (left side of the keyboard) corresponded to the green checkerboard. A detailed description of the test was published in previous papers written by our group (Schiff et al., 2005; Vallesi et al., 2005).

The variables considered were the mean RTs, the percentage of correct responses and the intra-individual variability of response speed, defined as the standard deviation of RTs. In addition, RTs were ranked from the fastest to the slowest and divided into quintiles (bins), separately for corresponding and non-corresponding trials, to analyze RT distribution and its relationship with pathology, task and P300 parameters.

Electrophysiological recordings

The electroencephalogram (EEG) was continuously recorded (Micromed System Plus, Mogliano Veneto, Italy) by 30 Ag/AgCl electrodes mounted on an elastic cap and positioned according to the international 10/20 system. The Fpz was used as the ground

and the reference was provided by the linked right and left mastoid electrodes. Two electrodes were placed on the external canthus and under the left eye to monitor horizontal and vertical eye movements (EOG), respectively. Each channel had its own analogue-to-digital converter (ADC). The EEG and EOG signals were digitalized on-line with a frequency rate of 512 Hz and a conversion resolution of 0.19 mV/digit. Impedance was kept lower than 5 kΩ. Signals were band-pass filtered between 0.03 and 30 Hz. The EEG epochs were extracted using a time-window analysis of 2300 ms (800 ms pre-stimulus and 1500 post-stimulus) and baseline corrected using a 200 ms pre-stimulus time interval. Epochs with excessive drift or containing eye movements/blinks were corrected using an independent component analysis (ICA) algorithm (Delorme & Makeig, 2004; Jung et al., 2001). A visual inspection was then performed in order to reject epochs with significant artefacts and only adequate epochs were subsequently considered for the analysis.

Estimation of single-trial P300 responses

During the last few years, different mathematical approaches have been proposed in order to derive ERP parameters, such as amplitude and latency, from single-trial EEG responses (Jaśkowski & Verleger, 2000; Jung et al., 2001; Rushby & Barry, 2009).

Here, a single-trial estimate was made using a Bayesian approach originally proposed by Sparacino and collaborators (Sparacino, Milani, Arslan, Cobelli, 2002) and further developed for P300 single-trial estimations by D'Avanzo and collaborators (2011), to which we refer the reader for details. Briefly, the method is formulated in two stages. In the first stage, each of the available raw sweeps is processed by an individual 'optimal' filter, determined using statistical information on the background EEG and on the unknown ERP obtained, respectively, from pre-stimulus and post-stimulus data. This avoids critical hypotheses on EEG and ERP stationarity. Then, a mean ERP is determined as the weighted average of the filtered sweeps, where each weight is proportional to the expected reliability of the sweep. In the second stage, single-sweep estimation is dealt with within the same framework by using the average ERP estimated in the previous stage as an a priori expected response. The P300 latency and amplitude were measured for each single trial. In addition, the mean P300 latency of all of the trials performed by each participant was computed, as well as its standard deviation, which was used as an index of IIV in P300.

Also, the mean latency and amplitude of P300 from each RT quintile was analysed in

order to determine the relationship between physiological measures and the RT distribution.

Statistics

Two types of analyses of variance (ANOVA) were run with group (first ANOVA: patients with cirrhosis vs. controls; second ANOVA: and patients with MHE vs. patients without MHE vs. controls) as between-subject factors and Simon task conditions (corresponding vs. non-corresponding) as within-subject factors. The P300 analysis also included the derivation (Pz, Cz, Fz) as a further within subject factor.

The ANOVA was also performed including the above mentioned group as between-subject factors and the Simon task condition (corresponding vs. non-corresponding) and the bin (RT in order of the fastest to the slowest and divided into five quintiles) as within-subject factors.

Two further repeated-measures ANOVAs were performed separately for P300 latency and amplitude, with the above-mentioned group as between-subject factors and the Simon task condition (corresponding vs. non-corresponding), the bin and the derivation as within-subject factors. Post-hoc analyses were carried out using Bonferroni tests.

Pearson's correlations were computed to evaluate the goodness of the fit of P300 parameter estimations with the Bayesian single-trial method and with those obtained using the conventional average.

A linear multiple regression analysis was run with the SDs of P300 latency and mean P300 amplitude (estimated using the Bayesian method) as predictors of the average-based P300 amplitude.

4.5.3 Results

Behavioural results

RTs

A main effect of correspondence (i.e. Simon effect) [F(1, 41)=33.39, p<0.001; η_p^2=0.45] was detected, revealing slower RTs in the non-corresponding condition than in the corresponding condition. Overall, the RTs were slower in patients with cirrhosis compared to the controls [F(1, 41)=12.98; p<0.001; η_p^2=0.24] and RTs in patients with MHE were slower than both in the controls and in patients without MHE [F(2, 40)=10.89; p<0.001; η_p^2=0.35], both in the corresponding and non-corresponding conditions (post-hoc test p<0.05; Table 4.7). No interaction was observed between group and correspondence [F(1, 41)=1.42; p=0.2; η_p^2=0.03] (see Table 4.7).

Response accuracy

Response accuracy was lower in non-corresponding trials compared to the corresponding ones [F(1, 41)=9.09, p<0.005; η_p^2=0.18]. Patients with cirrhosis showed a lower accuracy compared to the controls [F(1, 41)=5.69, p<0.05; η_p^2=0.12]; however, on closer inspection, the decrease in accuracy concerned only patients with MHE [F(2, 40)=5.64, p<0.01; η_p^2=0.2, post-hoc p<0.05)] (Table 4.7). Also in this case, the interaction between group and correspondence was not significant [F(1, 41)=0.49; p=0.6; η_p^2=0.02].

	Controls N=14	**All Patients** N=29	**Patients without MHE** N=13	**Patients with MHE** N=16
Mean RT corr (ms)	487 (63)	602 (119)	553 (103)	641 (119)
Mean RT non-corr (ms)	510 (67)	637 (117)	582 (105)	681 (109)
IIV. RT corr (ms)	110 (25)	144 (41)	130 (45)	156 (35)
IIV. RT non-corr (ms)	90 (18)	128 (37)	107 (30)	144 (35)
Accuracy corr (%)	97 (2)	90 (12)	95 (6)	87 (15)
Accuracy non-corr (%)	95 (4)	87 (12)	91 (8)	84 (13)

Table 4.7 Behavioral measures obtained from the Simon task in controls and patients. Mean (standard deviation).

Intra-individual variability in RTs

The IIV was greater in the corresponding condition compared to the non-corresponding condition [$F(1, 40)=23.96$, $p<0.0001$; $\eta_p^2=0.34$] (Table 4.7). Interestingly, the IIV in RT was higher in patients with cirrhosis compared to the controls (Table 4.7). Both patients with and without MHE had higher IIV than controls [$F(2, 40)=10.96$, $p<0.001$; $\eta_p^2=0.22$, post-hoc test $p<0.05$] (Figure 4.10A). No interaction was observed between group and correspondence factors [$F(1,41)=0.22$; $p<0.64$; $\eta_p^2=0.005$].

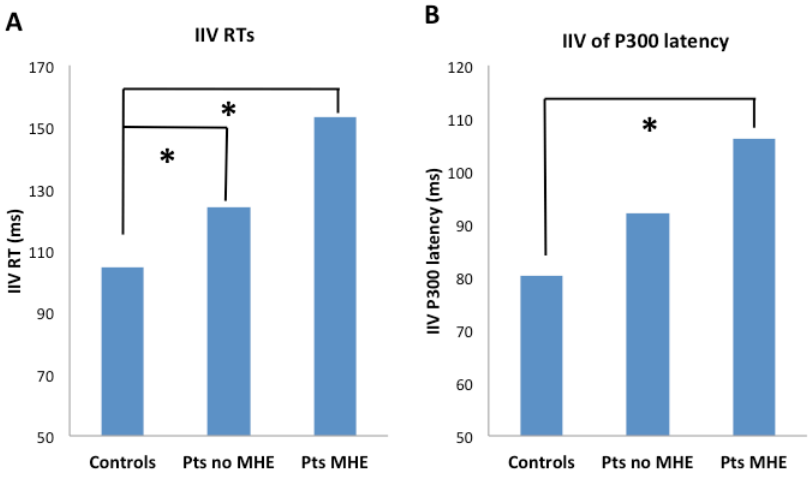

Figure 4.10 Panel A shows the means of IIV RT in the three groups of participants. The IIV progressively increased from normal individuals to patients with MHE (Bonferroni post-hoc test, $p<0.05$). **Panel B** shows the IIV in the single-trial estimated P300 latency in the three groups of participants. Patients with MHE showed a higher variability in latency than the control participants (post-hoc test $p<0.05$).

Distribution analysis of RTs

A dynamic image of IIV was provided by the study of reaction time (RTs) distribution via bin analysis. Together with the effect of bin [$F(4, 164)=304.00$, $p<0.0001$; $\eta_p^2=0.87$] and correspondence [$F(1, 41)=39.4$, $p<0.00001$; $\eta_p^2=0.47$], the interaction between correspondence and bin [$F(4, 160)=22.29$, $p<0.00001$; $\eta_p^2=0.33$] showed that the Simon effect decreased with slower RTs (Figure 4.11).

In agreement with the study of average RTs, the ANOVA test revealed a main effect of group [$F(1, 41)=13.0$, $p<0.001$]. Furthermore, a more relevant group per bin interaction was also found [$F(4, 164)=7.4$, $p<0.00005$; $\eta_p^2=0.12$]. This result indicated that the RTs were more scattered in patients with cirrhosis compared to the controls, especially when

the RTs were slower (post-hoc tests $p<0.05$). This effect was greater in patients with MHE than in those without MHE [$F(8, 160)=5.61$, $p<0.00001$; $\eta_p^2=0.21$, post-hoc tests $p<0.05$] (Figure 4.12). The bin per correspondence effect was observed in all groups whereas no interaction was observed between group, correspondence and bin [$F(8, 160)= 0.50$, $p=0.85$; $\eta_p^2=0.02$].

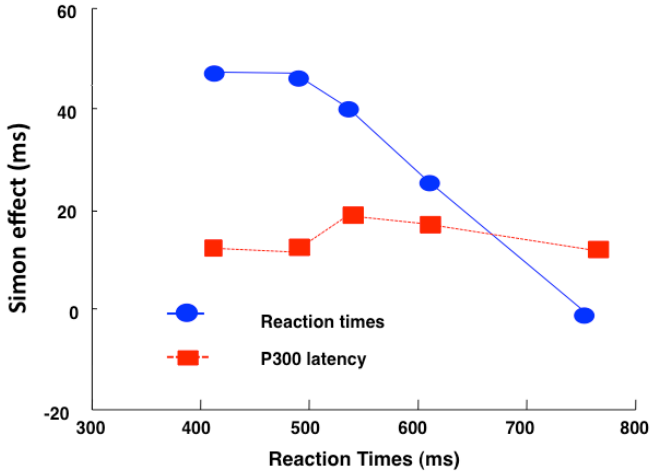

Figure 4.11 Distributional analysis of Simon effect: RTs and P300 latency data. From a behavioural point of view, the distributional analysis showed that the Simon effect (difference between non-corresponding and corresponding conditions) decreased with slower reaction times (continuous line). In contrast, as concerning P300 latency, the magnitude of the Simon did not change with longer RTs (dashed line).

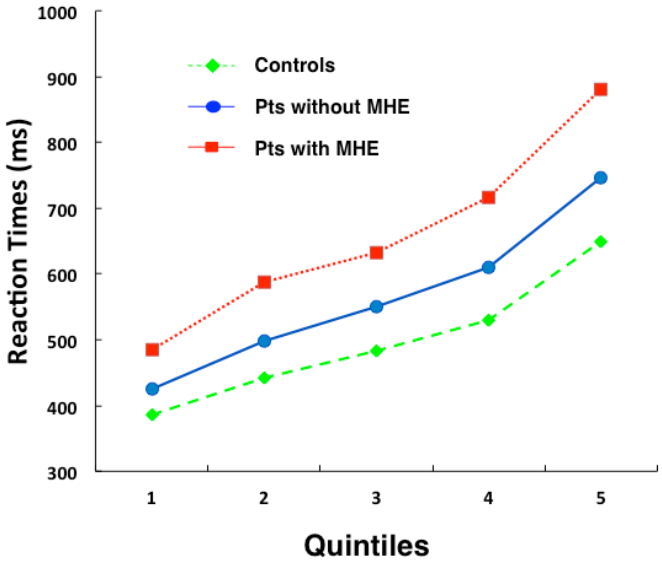

Figure 4.12 Distribution analysis of the reaction times (RTs) showed an interaction between group and bin. A larger variability in RTs, from fastest to slowest bin, can be seen in individuals with MHE compared to those without MHE.

P300 results

Average-based P300 measures

Overall, a trend of shorter latency of P300 in the corresponding compared to the non-corresponding condition was found [$F(1, 41)=3.71$, $p=0.06$; $\eta_p^2=0.8$] (Table 4.8). However, an additional analysis computed for the controls revealed that, in this group of participants, P300 latency was shorter in the corresponding condition compared to the non-corresponding condition [$F(1, 14)=5.52$, $p<0.05$; $\eta_p^2=0.30$]. No difference was observed in P300 latency between controls and patients [$F(1, 41)=0.09$, $p=0.74$; $\eta_p^2=0.003$] depending on correspondence [$F(1, 41)=1.51$, $p=0.17$; $\eta_p^2=0.04$] or derivation [$F(1, 41)=0.11$; $p=0.9$; $\eta_p^2=0.003$].

The P300 amplitude was lower in the non-corresponding condition compared to the corresponding condition [$F(1, 41)=18.77$, $p<0.0001$; $\eta_p^2=0.32$]; furthermore, an effect of derivation was found [$F(2, 82)=3.32$, $p<0.05$; $\eta_p^2=0.07$], showing that P300 was greater in the Pz compared to the Fz site. The interaction between correspondence and derivation [$F(2, 82)=3.20$, $p=0.05$; $\eta_p^2=0.07$] showed that the difference between the corresponding and non-corresponding conditions was greater in the Pz as compared to the Fz site (all $p<0.05$) (Table 4.8). Considering P300 amplitude, a main effect of group was detected [$F(1, 41)=12.95$, $p<0.001$; $\eta_p^2=0.24$], showing that P300 was smaller in patients with liver cirrhosis than in controls. In particular, P300 was smaller in patients with MHE compared to the controls but not compared to patients without MHE [$F(2, 40)=8.19$; $p<0.005$; $\eta_p^2=0.33$, post-hoc $p<0.05$]. No interaction of correspondence or derivation with the factor group was found (Table 4.8).

		Controls	All patients	Pat without MHE	Patients With MHE	Controls	All patients	Pat without MHE	Pat with MHE
		Latency (ms)				Amplitude (µV)			
AVG P300 corr	**Pz**	346 (56)	361 (71)	352 (52)	369 (69)	9.8 (4.6)	6.3 (3.2)	7 (3.1)	5.8 (3.3)
	Cz	359 (30)	374 (79)	354 (55)	390 (93)	9.7 (4.3)	5.5 (3.1)	7 (3.2)	4.5 (2.6)
	Fz	364 (20)	379 (74)	362 (42)	393 (92)	9.0 (3.4)	6.0 (3.0)	7 (3.0)	4.5 (1.9)
AVG P300 noncorr	**Pz**	360 (65)	365 (103)	347 (104)	378 (102)	9.0 (3.5)	5.4 (2.8)	6.0 (3.0)	4.9 (2.6)
	Cz	388 (37)	377 (76)	366 (41)	386 (95)	8.8 (3.7)	4.7 (2.9)	5.8 (3.0)	3.9 (2.7)
	Fz	373 (32)	379 (86)	367 (40)	388 (111)	7.9 (2.9)	5.1 (2.8)	6.4 (2.9)	4.0 (2.3)
Single trial P300 corr	**Pz**	365 (31)	377 (36)	370 (37)	383 (36)	12.6 (4.2)	9.6 (3.4)	9.8 (3.4)	9.4 (3.4)
	Cz	375 (27)	387 (32)	377 (27)	394 (37)	12.7 (4.3)	8.9 (2.9)	9.6 (3.3)	8.0 (2)
	Fz	366 (20)	382 (34)	370 (25)	392 (38)	11.4 (3.6)	8.9 (2.6)	9.7 (3.3)	8.3 (1.7)
Single trial P300 noncorr	**Pz**	385 (40)	391 (43)	388 (53)	397 (34)	12.0 (3.4)	9.1 (3)	9.4 (3.2)	8.8 (3.0)
	Cz	393 (34)	405 (34)	396 (29)	412 (37)	12.4 (3.8)	8.7 (3)	9.4 (3.3)	8.1 (2.6)
	Fz	384 (26)	394 (34)	383 (31)	403 (33)	11.3 (3.3)	8.8 (2.7)	9.0 (3.2)	8.2 (2.2)

Table 4.8 Average-based and single-trial estimated P300 latencies and amplitudes in Pz, Cz, Fz. Mean (standard deviation).

Single trial-based P300 measures

Single-trial P300 latency was clearly shorter in the corresponding condition compared to the non- corresponding condition [$F(1, 41)=76.54$, $p<0.00001$; $\eta_p^2=0.65$]. A significant effect of derivation was found [$F(2, 41)=3.57$, $p<0.05$; $\eta_p^2=0.08$], showing that P300 latency was higher in the Pz compared to the Fz site (post-hoc test $p<0.05$). In agreement with the results observed using the averaged-based P300 analysis, single-trial P300 latency did not differ between the controls and the patients with cirrhosis, with or without MHE [$F(2, 82)=1.29$, $p=0.26$; $\eta_p^2=0.03$] (Table 4.8). No interaction was found between correspondence or derivation and the factor group.

Overall, the P300 amplitude was lower in the non-corresponding condition compared to the corresponding conditions [$F(1, 41)=5.57$, $p<0.05$; $\eta_p^2=0.12$). As observed above with the average- based P300 analyses, a significant site per correspondence interaction was found [$F(2, 82)=7.51$, $p<0.005$; $\eta_p^2=0.16$], showing that the difference between corresponding and non-corresponding conditions was greater in the Pz site compared to both the Fz and Cz sites (all $p<0.001$) (Table 4.8). The P300 amplitude was smaller in patients with cirrhosis compared to the controls [$F(1, 41)=9.19$, $p<0.005$; $\eta p2=0.18$].

Patients with MHE had a lower P300 amplitude compared to the controls [$F(2, 40)=5.07$, $p<0.05$; $\eta_p^2=0.19$, post-hoc test $p<0.05$] (Table 4.8). No interaction was found between correspondence or derivation and the factor group.

Relationship between average-based and single trial-based P300 measures

The average-based and single-trial P300 latencies, as well as the average-based and single-trial P300 amplitudes measured in Pz, were found to be correlated ($r=0.72$, $p<0.0001$ and $r=0.90$, $p<0.0001$, respectively). Furthermore, the averaged-based P300 amplitude was found to be inversely correlated with IIV single-trial P300 latency ($r=-7.3$, $p<0.0001$), thus showing that the higher the IIV of P300 latency, the lower the average-based P300 amplitude. On closer inspection, multivariate regression analysis showed that the averaged-based P300 amplitude was predicted by both the IIV of single-trial P300 latency (Beta=-0.25±0.04 (SE); $p<0.0001$) and single-trial amplitude (Beta=-0.78±0.04; $p<0.0001$). When performing the same analysis separately for the controls and patients, it became evident that both the IIV in P300 latency (Beta=-0.33±0.06, $p<0.0001$ and Beta=-0.16±0.06, $p<0.05$, in cirrhotic patients and the controls, respectively), and single-trial P300 amplitude (Beta=-0.73±0.06, $p<0.0001$, and Beta=-0.85±0.07, $p<0.0001$, in cirrhotic patients and the controls, respectively) affected the amplitude of the average-based P300 amplitude. However, as suggested by the ratio between the Beta's and their standard errors, the contribution of P300 latency jittering to the average-based P300 amplitude was twice as high in patients with cirrhosis compared to the controls: 5 and 2.3, respectively.

		Controls	All patients	Patients Without MHE	Patients with MHE
	Electrode			**Latency (ms)**	
IIV P300 corr	**Pz**	77 (23)	94 (20)	87 (19)	99 (20)
IIV P300 non-corr	**Pz**	83 (21)	106 (22)	97 (23)	111 (19)
IIV P300 corr	**Cz**	79 (18)	98 (19)	89 (17)	104 (18)
IIV P300 non-corr	**Cz**	82 (16)	104 (20)	97 (17)	110 (21)
IIV P300 corr	**Fz**	80 (17)	93 (20)	84 (18)	101 (20)
IIV P300 non-corr	**Fz**	85 (15)	100 (20)	92 (15)	106 (22)

Table 4.9 IIV of P300 latency obtained by single trial estimate in the derivations Pz, Cz, Fz. Mean (standard deviation).

Intra-individual variability of P300

The IIV in P300 latency was higher in the non-corresponding condition compared to the corresponding condition [$F(1, 41)=11.23$, $p<0.005$; $\eta_p^2=0.21$]. Furthermore, a derivation per correspondence interaction was found [$F(2, 82)=5.45$, $p<0.01$ $\eta_p^2=0.12$], showing that the difference in P300 latency jittering between the corresponding and non-corresponding trials was greater in the Pz site (post-hoc $p<0.05$).

A higher IIV in the P300 latency was evidenced in patients with cirrhosis compared to the controls [$F(1, 41)=10.35$, $p<0.005$; $\eta_p^2=0.20$]. This effect was detectable in patients with MHE [$F(2, 39)=7.8721$, $p=0.005$; $\eta_p^2=0.28$, post-hoc test $p<0.05$] (Table 4.9, Figure 4.10B and Figure 4.13B); in contrast, the post-hoc test comparison between controls and patients without MHE did not reach statistical significance ($p=0.08$). No interaction was found between the IIV in P300 latency and group [$F(1, 41)=1.1$, $p=0.3$; $\eta_p^2=0.02$].

The IIV in P300 amplitude was higher in the Cz site compared to both the Pz and Fz sites [$F(2, 82)=7.95$, $p<0.001$; $\eta_p^2=0.16$, post-hoc $p<0.05$]. The statistical tests did not reveal any other significant effect of IIV in P300 amplitude concerning factor correspondence [$F(1, 41)=0.37$, $p=0.85$; $\eta_p^2=0.001$] or group [$F(1, 41)=0.35$, $p=0.54$; $\eta_p^2=0.01$].

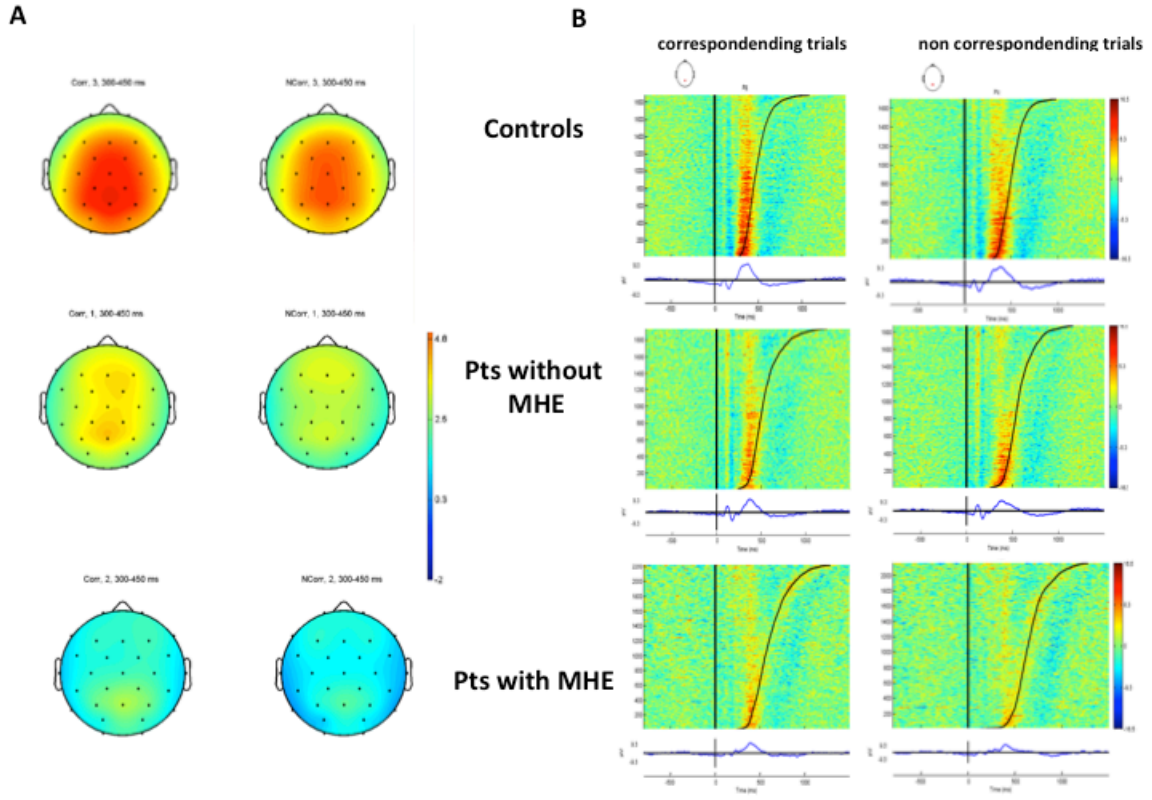

Figure 4.13 Panel A: P300 scalp voltage distributions in the three groups are shown for the corresponding and non-corresponding trials. Panel B: Colour plots of single-trial P300 responses in Pz are depicted ordered based on RT speed (black curves), from the fastest to the slowest, in the three group of patients. The patients with cirrhosis show an increased IIV in P300 latency, a reduction in P300 amplitude (both in corresponding and non-corresponding conditions) and a loss of the relationship between P300 and behavioural responses.

Relationship between single-trial P300 and reaction time distribution

Regarding P300 latency, main effects of correspondence [$F(1, 41)=75.78$, $p<0.00001$; $\eta_p^2=0.65$] and bin [$F(4, 164)=8.49$, $p<0.005$; $\eta_p^2=0.17$] were detected. The effect of bin revealed that P300 latency increased with longer RTs. Unlike with RT, no interaction was found between correspondence and bin [$F(4, 164)=0.97$, $p=0.4$; $\eta_p^2=0.02$]; see Figure 4.11. Furthermore, a more relevant group per bin interaction was found [$F(4, 164)=7.05$, $p<0.00005$; $\eta_p^2=0.15$], showing that the relationship between P300 latency and RT was closer and steeper in the controls than in the patients with cirrhosis, especially in patients with MHE (Figure 4.14B). On closer inspection it became evident that in patients with MHE the relationship between RT and P300 latency was completely lost [$F(8, 160)=5.14$, $p<0.00001$; $\eta_p^2=0.20$; all $p<0.05$]; see Figure 4.14A.

The relationship between P300 amplitude and RT distribution highlighted the main

effects of correspondence [F(1, 41)=4.47, p<0.05; η_p^2=0.11], bin [F(4, 164)=37.92, p<0.0001; η_p^2=0.48], and derivation [F(2, 82)=4.98, p<0.01; η_p^2=0.48]. The effect of bin showed that the P300 amplitude decreased with increasing RTs. A site per bin interaction was also found, showing that the decrease in amplitude with slower RTs was greater for the Pz and Cz sites compared to the Fz site (post-hoc p< 0.05). Furthermore, a more relevant effect of group [F(1, 41)=8.71, p<0.01; $\eta_p^2$2=0.18] and the significant interaction between group and bin [F(4, 164)=3.57, p<0.01; η_p^2=0.08] showed that the P300 amplitude decreased with longer RTs in controls, whereas such a relationship was weaker in patients with cirrhosis, who showed longer RTs. Specifically, the post-hoc tests clearly showed the lack of a relationship between the P300 amplitude and RTs in patients with MHE [F(8, 160)=2.7, p<0.01; η_p^2=0.12]; see Figures 4.13B and 4.14B.

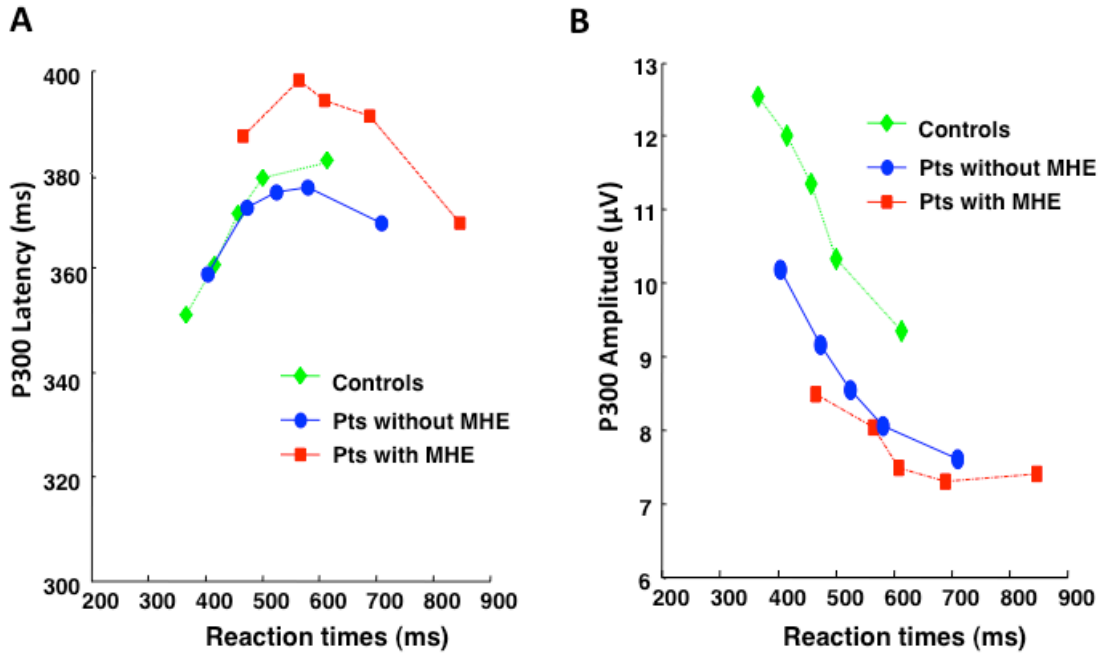

Figure 4.14 Panel A: Analysis of the time course of P300 latency along the RT distribution shows an interaction between group and bin. This proved that in normal controls the P300 latency increased with slower RTs. This relationship can also be observed in patients without MHE but only when the RTs overlap those of the controls (i.e. quintiles 1, 2 and 3). In contrast, the relationship between P300 latency and RTs disappears in patients with MHE, suggesting that delayed RTs depend on some processes that follow the P300 component. **Panel B: Relationship between P300 amplitude and RTs distribution.** The interaction between group and bin shows that the P300 amplitude decreased with increasing RTs in the controls but not in the cirrhotic patients.

4.5.4 Discussion

In the present study, single-trial P300 parameters, obtained during execution of the S-R conflict Simon task, were estimated in order to investigate the IIV of P300 as a marker of brain dysfunction in MHE. Furthermore, the present research highlighted the power of single-trial ERP analyses in the study of the dynamic relationship between electrophysiological parameters and RT distribution under both normal and pathological conditions.

Overall, the patients with liver cirrhosis, especially those with MHE, showed longer RTs and reduced response accuracy compared to controls. Furthermore, the IIV in RT was greater in patients with cirrhosis, both with and without MHE, compared to the controls. The Simon effect (i.e., slower RTs in the non-corresponding condition compared to the corresponding condition) was detected both in controls and patients with cirrhosis and was equivalent between the two groups.

The electrophysiological results confirmed the sensitivity of P300 latency and amplitude to stimulus-response correspondence (e.g., Valle-Inclan, 1996): a longer P300 latency and a smaller P300 amplitude in the non-corresponding condition compared to the corresponding condition were observed in both healthy controls and patients with cirrhosis.

The patients with cirrhosis showed a reduced P300 amplitude compared to the controls. In contrast, P300 latency did not differ between patients with cirrhosis and controls. Usually, a reduction in amplitude is considered to be the electrophysiological counterpart of reduced cortical activation due to a central nervous system dysfunction (Walhovd et al., 2008). However, given the presence of increased IIV in RTs in patients with MHE, the possibility that a reduction in the P300 amplitude, as measured by the conventional averaging technique, might also be due to the increased IIV in the single-trial P300 latency (i.e. greater latency jittering – Mouraux & Iannetti, 2008) cannot be excluded. Overall, greater within-person variability in P300 latency was found in patients with MHE compared to healthy controls. In general, the P300 amplitude, obtained using the averaging technique, was found to be related to both the single-trial P300 amplitude and to P300 latency variability, both in controls and in patients with cirrhosis. Notably, the effect of P300 latency jittering was double in patients with MHE. These findings respond to the first two issues developed in the present study. Indeed they suggest that a condition of brain dysfunction, as observed in the case of patients with MHE, might cause an increase in the variability of P300 latency, which in turn might be responsible for the attenuation of P300

amplitude. It can be hypothesized that such a dysfunction occurring in MHE is implicated in increasing the variability in the synchrony of the firing rate of large neuronal populations, which would lead to increase the variability of post-synaptic neural responses and behavioural response speed. Interestingly, a similar mechanism linking neurons and astrocyte functioning was recently suggested in order to explain increased IIV in behavioural speed and RT slowness in individuals with ADHD (Russell et al., 2006).

The distributional analysis of RTs showed that, in control participants, the Simon effect decreased in magnitude as the RTs increased, confirming previous observations in the literature (De Jong, Liang, Lauber, 1994; Ridderinkhof, 2002, Vallesi et al., 2005). In order to explain this phenomenon, one of the most influential hypotheses suggests the presence of an inhibitory mechanism that progressively impinges on the incorrect response activated by the irrelevant spatial positioning of the target stimulus (Ridderinkhof, 2002, for a review see Proctor, Miles, & Baroni, 2011). The inhibitory mechanism is supposed to mainly act on later response selection/execution stages, thus it should be less sensitive to stimulus processing, or to decisions related to the automatic stimulus-response association. This consideration is supported by recent fMRI and EEG studies, which showed activation of the right inferior frontal gyrus only with slower RTs when the Simon effect decreased (Forstmann, Van den Wildenberg, & Ridderinkhof). Interestingly, the decay of the Simon effect was also detectable in patients with cirrhosis regardless of the presence of MHE, suggesting that the late inhibitory process is also preserved in patients with clear signs of psychomotor slowing.

Overall, patients with cirrhosis, especially those with MHE, showed a greater difference between slowest and fastest RTs when compared to the healthy controls. These data suggest a difference in the slopes of RT distribution. The RT can be described by an ex-Gaussian distribution: a Gaussian-like distribution with a longer left-sided tail. This kind of distribution is the result of the convolution of a Gaussian and an exponential distribution. The mode and standard deviation of the Gaussian component are approximated by μ and d, respectively, while the exponential function is approximated by t, which reflects the mean and standard deviation of the exponential component. Balota and Yap (2011) suggested that a difference in the slopes of RT distribution is a sign of a difference in t or, in other terms, in the skew of the two RT distributions. These data confirm previous observations regarding increased variability in reaction speed in cirrhotic patients (Elsass et al., 1985; Schiff et al., 2006).

The study of the relationship between RT distribution and single-trial P300 parameters showed that, although P300 is sensitive to stimulus-response correspondence, unlike behavioural speed, a decay of the Simon effect in terms of P300 latency differences was not detectable with longer RTs. This effect was also observed in patients with cirrhosis and, in agreement with Verleger and collaborators (2005), suggests that P300 is sensitive to early coding of the stimulus-response association but independent to the inhibitory processes acting on later response-related processing stages. To the best of our knowledge, this finding defines, for the first time, a clear boundary concerning the relationship between P300 parameters and behavioral response during the execution of a conflict task.

Overall, in normal participants, P300 latency increased and amplitude decreased with increasing RTs. Interestingly, these relationships were weaker in the cirrhotic patients without MHE and were completely absent in patients with MHE. These results suggest that, under normal conditions, the relationship between P300 and RTs is detectable and matches the individual's performance. In contrast, when brain does not properly work due to metabolic dysfunction, as in patients with MHE, single-trial P300 responses are reduced in strength and their latency jittering is increased. As a consequence of these alterations, patients with MHE show an increase in RTs compared to controls and a loss of the relationship strength between RTs and single-trial P300 parameters.

The results of the present research support the hypothesis that behavioural measures of the IIV in response speed are a useful indicator of pathological performance. Furthermore, they indicated that single-trial ERP analysis is a powerful technique for studying IIV in electrophysiological measures in both clinical and basic research.

GENERAL CONCLUSIONS

In the present thesis, five experiments were run in order to identify the cognitive and the electrophysiological alterations in normal aging and in minimal hepatic encephalopathy.

In the first part of the thesis, it was explored the possible role of executive control in determining age-related deficits by investigating the ERPs elicited in a PM task (Experiment 1) and in the ICT (Experiment 2). Both the experiments converged in revealing that executive control, as unitary concept, was not able to account for the age-related differences evidenced by the tasks. The analysis of the ERPs showed several electrophysiological changes that were more likely attributable to age-related alterations in basic mechanisms (rather than executive dysfunctions). In particular, findings from Experiment 1 suggest that the impairment observed in PM performance by older individuals was due to a reduction in the availability of controlled resources required for adequately executing the ongoing and the PM tasks together. This suggestion was driven by the fact that older adults recruited a large amount of processing resources even to perform the ongoing activity alone, as indexed by the anterior shift of P3 already in the baseline block. Therefore, in the PM block, they had fewer resources available to adequately maintain the PM intentions in mind in the PM block. In such a way, older adults would not have alterations in goal maintenance process per se (as postulated by the theory of cognitive control, Braver & West, 2008), but rather a general reduction in the amount of cognitive resources allocated, as proposed by Craik's theory (1986).

Likewise, results from Experiment 2 indicated that age-related differences in ICT performance could not be explained by deficits in executive control, as a unitary function, but rather by a more low-level mechanism that is the general reduction in processing speed (giving in part support to Salthouse's theory, 1996). However, the analysis of ERPs highlighted that, among the three processes composing the executive control, attentional switching is likely the most vulnerable to aging. This claim was driven by the findings on RON components, which were delayed and attenuated in older respect to younger adults.

In conclusion, findings of the first part of the present thesis suggest that age-related deficits in cognitive tasks are due both to a reduced speed of processing and to an impairment in a specific subprocess of executive control.

In the second part of the thesis, the cognitive and the ERP alterations associated with MHE were examined. In Experiments 3 and 4, the ICT was employed since it allows to assess several cognitive processes, including attention, working memory updating and inhibition. MHE seems to affect particularly sustained and selective attention functions, as revealed by the prolongation and reduction of the P300 elicited in the detect trials. Moreover, these findings suggest that the impairment of the attentional functions might be the primary cause of the worse performance observed also in the ICT trials requiring higher cognitive functions (i.e., working memory updating and response inhibition). Therefore, testing low-level functions, such as attention, seems to be the best way for the diagnosis of MHE. Experiment 4 highlighted that patients without MHE displayed an enhancement (instead of a decrease) in several ERP components (i.e., N2 and P3-nogo). This might indicate the recruitment of compensatory mechanisms in patients who did not reveal any sign of brain dysfunction (even when assessed with the sophisticated psychometric and EEG tools). These findings are noteworthy as they suggest the need to open a debate about the definition of the boundary between the presence and the absence of MHE.

Finally, Experiment 5 evidenced how MHE was associated with an increase of intra-individual variability of P300 latency. This increase seemed to determine, at least in part, the reduction in the P300 amplitude, and was revealed to be a good index of brain dysfunction. Another sign of neural alteration was the weaker relationship between RTs and P300 parameters observed in patients with MHE.

In summary, all the experiments carried out in the present thesis converged in highlighting that both normal and pathological aging, as investigated in the studies of the present thesis, affect particularly the basic cognitive mechanisms, such as the availability and the speed of cognitive processes, as well as the sustained and selective attention. The analysis of ERPs was revealed to be a powerful technique to address this issue.

References

Adrover-Roig, D., & Barcelo, F. (2010). Individual differences in aging and cognitive control modulate the neural indexes of context updating and maintenance during task switching. *Cortex, 46,* 434–450.

Alin, A., Kurt, S., McIntosh, A. R., Öniz,A., & Özgören, M. (2009). Partial least squares analysis in electrical brain activity. *Journal of Data Science*, *7*, 99–110.

Allport, A., & Wylie, G. (2000). Task-switching, stimulus- response bindings, and negative priming. In S. Monsell & J. S. Driver (Eds.), *Control of cognitive processes. Attention and performance XVIII*. Cambridge, MA: MIT Press.

Altmann, E.M. (2002). Functional decay of memory for tasks. *Psychological Research, 66,* 287–297.

Amodio, P., & Gatta, A. (2005). Neurophysiological investigation of hepatic encephalopathy. *Metabolic brain disease*, *20*(4), 369–79.

Amodio, P., Campagna, F., Olianas, S., Iannizzi, P., Mapelli, D., Penzo, M., Angeli, P., … Gatta, A. (2008). Detection of minimal hepatic encephalopathy : Normalization and optimization of the Psychometric Hepatic Encephalopathy Score. A neuropsychological and quantified EEG study. *Practice, 49,* 346–353.

Amodio, P., Del Piccolo, F., Pettenò, Mapelli, D., Angeli, P., Iemmolo, R., Muraca, M., Musto, C., Gerunda, G., Rizzo, C., Merkel, C., & Gatta, A. (2001). Prevalence and prognostic value of quantified electroencephalogram (EEG) alterations in cirrhotic patients. *Journal of Hepatology*, *35*, 37–45.

Amodio, P., Marchetti, P., Del Piccolo, F., Beghi, A., Comacchio, F., Carraro, P., Campo, G., Baruzzo, L., Marchiori, C., & Gatta, A. (1997). The effect of flumazenil on subclinical psychometric or neurophysiological alterations in cirrhotic patients: A double-blind placebo-controlled study. *Clinical Physiology,17,* 533–539.

Amodio, P., Marchetti, P., Del Piccolo, F., Campo, G., Rizzo, C., Iemmolo, R.M., Gerunda, G., Caregaro, L., Merkel, C., & Gatta, A. (1998a). Visual attention in cirrhotic patients: A study on

covert visual attention orienting. *Hepatology, 27,* 1517–1523.

Amodio, P., Marchetti, P., Del Piccolo, F., de Tourtchaninoff, M., Varghese, P., Zuliani, C., Campo, G., Gatta, A., & Guerit, J.M. (1999). Spectral versus visual EEG analysis in mild hepatic encephalopathy. *Clinical Neurophysiology, 110,* 1334–1344.

Amodio, P., Marchetti, P., Del Piccolo, F., Rizzo, C., Iemmolo, R.M., Caregaro, L., Gerunda, G., & Gatta, A. (1998b). Study on the Sternberg paradigm in cirrhotic patients without overt hepatic encephalopathy. *Metabolic Brain Disease,13,* 159–172.

Amodio, P., Montagnese, S., Gatta, A., & Morgan, M. Y. (2004). Characteristics of minimal hepatic encephalopathy. *Metabolic brain disease*, *19*(3-4), 253–267.

Amodio, P., Quero, J.C., Del Piccolo, F., Gatta, A., & Schalm, S.W. (1996). Diagnostic tools for the detection of subclinical hepatic encephalopathy: Comparison of standard and computerized psychometric tests with spectral-EEG. *Metabolic Brain Disease,11,* 315–327

Amodio, P., Schiff, S., Piccolo, F. D., Mapelli, D., Gatta, A., & Umiltà, C. (2005). Attention Dysfunction in Cirrhotic Patients: An Inquiry on the Role of Executive Control, Attention Orienting and Focusing. *Metabolic Brain Disease*, *20*(2), 115–127.

Anderson, J.R., & Bower, G.H. (1973). *Human Associative Memory.* Wiley, New York.

Andrés, P., Guerrini, C., Phillips, L., & Perfect, T. J. (2008). Differential effects of aging on executive and automatic inhibition. *Developmental Neuropsychology*, *33(2)*, 1–23.

Anguera, J. A., & Gazzaley, A. (2011). Dissociation of motor and sensory inhibition processes in normal aging. *Clinical Neurophysiology*. International Federation of Clinical Neurophysiology.

Arias, J.L., Aller, M.-A., Sánchez-Patan, F., & Arias, J. (2006). The inflammatory bases of hepatic encephalopathy. *European journal of gastroenterology & hepatology*, *18*(12), 1297–1310.

Aron, A.R., 2007. The neural basis of inhibition in cognitive control. *The Neuroscientist*, *13*, 1–15.

Aron, A.R., Behrens, T.E., Smith, S., Frank, M.J., & Poldrack, R.A. (2007). Triangulating a cognitive control network using diffusion-weighted magnetic resonance imaging (MRI) and functional MRI. *Journal of Neuroscience, 27,* 3743–3752.

Backman, L., Almkvist, O., Andersson, J., Nordberg, A., Winblad, B., Reineck, R., & Langstrom, B. (1997). Brain activation in young and older adults during implicit and explicit retrieval. *Journal of Cognitive Neuroscience, 9,* 378–391.

Bahn, E., Nolte,W., Kurth, C., Ramadori, G., Ruther, E., & Wiltfang, J. (2002). Quantification of the electroencephalographic theta/alpha ratio for the assessment of portal-systemic encephalopathy following implantation of transjugular intrahepatic portosystemic stent shunt (TIPSS). *Metabolic Brain Disease,17,*19–28.

Bajaj, J. S., Hafeezullah, M., Franco, J., Varma, R. R., Hoffmann, R. G., Knox, J. F., Hischke, D., et al. (2008a). Inhibitory control test for the diagnosis of minimal hepatic encephalopathy. *Gastroenterology*, *135*(5), 1591–1600.

Bajaj, J. S., Hafeezullah, M., Hoffmann, R. G., Varma, R. R., Franco, J., Binion, D. G., Hammeke, T. A. & Saeian, K. (2008b), Navigation skill impairment: Another dimension of the driving difficulties in minimal hepatic encephalopathy. *Hepatology, 47,* 596–604.

Bajaj, J. S., Hafeezullah, M., Hoffmann, R. G., Varma, R. R., Franco, J., Binion, D. G., Hammeke, T. A. & Saeian, K. (2008b), Navigation skill impairment: Another dimension of the driving difficulties in minimal hepatic encephalopathy. *Hepatology, 47,* 596–604.

Bajaj, J. S., Saeian, K., Verber, M. D., Hischke, D., Hoffmann, R. G., Franco, J., Varma, R. R., et al. (2007). Inhibitory control test is a simple method to diagnose minimal hepatic encephalopathy and predict development of overt hepatic encephalopathy. *The American journal of gastroenterology*, *102*(4), 754–60.

Bajaj, J. S., Schubert, C. M., Heuman, D. M., Wade, J. B., Gibson, D. P., Topaz, A., Saeian, K., Heuman, D.M., Wade, J.B., Hafeezullah, M., Bell, D.E., Sterling, R.K., Stravitz, R.T, Luketic, V., White, M.B., & Sanyal., A.J. (2010). Persistence of cognitive impairment after resolution of overt hepatic encephalopathy. *Gastroenterology, 138(7),* 2332-40.

Bajaj, J. S., Wade, J. B., & Sanyal, A. J. (2009). Spectrum of neurocognitive impairment in

cirrhosis: Implications for the assessment of hepatic encephalopathy. *Hepatology, 50*(6), 2014–21.

Bajaj, J.S., Hafeezullah, M., Franco, J., Joshua, F.K, Varma, R.R, Hammeke, T.A., Pinkerton, S., Hoffmann, R.G., & Saeian, K. (2008a). Inhibitory control test for the diagnosis of minimal hepatic encephalopathy. *Gastroenterology, 135*, 1591–1600.

Balota, D.A. & Yap, M.J. (2011). Moving Beyond the Mean in Studies of Mental Chronometry: The Power of Response Time Distributional Analyses. *Current directions in Psychological Science*, *20*, 160-166.

Baltes, P. B., & Lindenberger, U. (1997). Emergence of a powerful connection between sensory and cognitive functions across the adult life span: A new window to the study of cognitive aging? *Psychology and Aging, 12(1),* 12–21.

Baltes, P. B., & Smith, J. (1997). A systemic-wholistic view of psychological functioning in very old age: Introduction to a collection of articles form the Berlin Aging Study. *Psychology and Aging*, *12,* 395–409.

Baltes, P. B., Staudinger, U. M., Maercker, A. & Smith, J. (1995). People nominated as wise: a comparative study of wisdom-related knowledge. *Psychology of Aging, 10,* 155–166.

Barceló, F. (2003). The Madrid Card Sorting Test (MCST): A task switching paradigm to study executive attention with event-related potentials. *Brain Research Protocols, 11(1),* 27–37.

Barceló, F., Perianez, J. A., & Knight, R. T. (2002). Think differently: A brain orienting response to task novelty. *NeuroReport, 13(15),* 1887–1892.

Bargh, J.A., & Chartrand, T.L. (1999). The unbearable automaticity of being. *American Psychology. 54*, 462–479.

Barrett, G., Neshige. R., & Shibasaki, H. (1987). Human auditory and somatosensory event-related potentials: effects of response condition and age. *Electroencephalography and clinical Neurophysiology, 66(4),* 409–419.

Bastin, C., & Meulemans, T. (2002). Are time-based and event-based prospective memory

affected by normal aging in the same way? *Current Psychology Letters: Behaviour, Brain & Cognition, 7,* 105–121.

Bäumler, G. (1974). Lern-und Gedaechtnistes (LGT-3): Handanweisung. Hogrefe, Goettingen, Germany.

Bedard, A C., Nichols, S., Barbosa, J. A., Schachar, R., Logan, G. D., & Tannock, R. (2002). The development of selective inhibitory control across the life span. *Developmental Neuropsychology, 21,* 93–111.

Bellgrove, M.A., Hester, R., & Garavan, H. (2004). The functional neuroanatomical correlates of response variability: evidence from a response inhibition task. *Neuropsychologia*, *42*, 1910-1916.

Benjamini, Y., & Hochberg, Y. (1995). Controlling the False Discovery Rate: A Practical And Powerful Approach to Multiple testing. *Journal of the Royal Statistical Society. B*, *57(1),* 289-300.

Benjamini, Y., & Yekutieli, D. (2001). The control of the false discovery rate in multiple testing under dependency, *Annals of Statistics* 29, 1165–1188.

Berti, S. (2008a). Cognitive control after distraction: event-related brain potentials (ERPs) dissociate between different processes of attentional allocation. *Psychophysiology*, *45*(4), 608–620.

Berti, S. (2008b). Object switching within working memory is reflected in the human event-related brain potential. *Neuroscience letters*, *434*(2), 200–5.

Berti, S., & Schroger, E. (2001). A comparison of auditory and visual distraction effects: behavioral and event-related indices. *Cognitive Brain Research*, *10*, 265–273.

Berti, S., & Schröger, E., (2003). Working memory controls involuntary attention switching: evidence from an auditory distraction paradigm. *European Journal of Neuroscience*, *17*, 1119–1122.

Berti, S., Roeber, U., & Schröger, E., (2004). Bottom-up influences on working memory:

behavioral and electrophysiological distraction varies with distractor strength. *Experimental Psychology*, *51*, 249–257.

Beste, C., Willemssen, R., Saft, C., & Falkenstein, M. (2009). Error processing in normal aging and in basal ganglia disorders. *Neuroscience, 159,* 143–149.

Beste, C., Willemssen, R., Saft, C., & Falkenstein, M. (2010). Neuropsychologia Response inhibition subprocesses and dopaminergic pathways : Basal ganglia disease effects. *Neuropsychologia*, *48*, 366–373.

Bisiacchi, P. S. (1996). The neuropsychological approach in the study of prospective memory. In M. Brandimonte, G. O. Einstein, & M. A. McDaniel (Eds.), *Prospective memory: Theory and applications*. Mahwah, NJ: Lawrence Erlbaum Associates. 297–317.

Bisiacchi, P. S., Cona, G., Schiff, S., & Basso, D. (2011). Modulation of a fronto-parietal network in event-based prospective memory: An rTMS study. *Neuropsychologia*, *49*, 2225–2232.

Bisiacchi, P. S., Schiff, S., Ciccola, A., & Kliegel, M. (2009). The role of dual-task and task-switch in prospective memory: Behavioural data and neural correlates. *Neuropsychologia*, *47*, 1362 – 1373.

Bisiacchi, P. S., Tarantino, V., & Ciccola, A. (2007). Aging and prospective memory : the role of working memory and monitoring processes. *Aging*, *20*(6), 569–577.

Botvinick, M. M., Braver, T. S., Barch, D. M., Carter, C. S., & Cohen, J. D. (2001). Conflict monitoring and cognitive control. *Psychological Review, 108(3),* 624–652.

Brandimonte, M. A., Einstein, G. O., & McDaniel, M. A. (1996). *Prospective memory: Theory and applications*. Mahwah, NJ: Erlbaum.

Braver, T. S., & Barch, D. M. (2002). A theory of cognitive control, aging cognition, and neuromodulation. *Neuroscience and biobehavioral reviews*, *26*(7), 809–17.

Braver, T. S., Barch, D.M., Keys, B. A., Carter, C. S., Cohen, J. D., Kaye, J. A. … Reed, B. (2001). Context processing in older adults: Evidence for a theory relating cognitive control to neurobiology in healthy aging. *Journal of Experimental Psychology: General, 130,* 746–763.

Braver, T. S., Cohen, J. D., & Barch, D. M. (2002). The role of the prefrontal cortex in normal and disordered cognitive control: A cognitive neuroscience perspective. In D. T. Stuss & R. T. Knight (Eds.), *Principles of frontal lobe function* (pp. 428–448). Oxford, England: Oxford University Press.

Braver, T. S., Gray, J. R., & Burgess, G. C. (2007). Explaining the many varieties of working memory variation: Dual mechanisms of cognitive control. In A. Conway, C. Jarrold, M. Kane, A. Miyake & J. Towse (Eds.), *Variation in working memory*. Oxford, England: Oxford University Press.

Braver, T. S., Paxton, J. L., Locke, H. S., & Barch, D. M. (2009). Flexible neural mechanisms of cognitive control within human prefrontal cortex. *Proceedings of the National Academy of Sciences of the United States of America*, *106*(18), 7351–6.

Braver, T.S., & West, R. (2008). Working memory, executive control, and aging. In F. I. Craik & T. Salthouse (Eds.), *The handbook of aging and cognition* (3rd ed, pp. 311–372). New York, NY: Psychology Press.

Braver, T.S., Satpute, A.B., Keys, B.A., Racine, C.A., & Barch, D.M. (2005). Context processing and context maintenance in healthy aging and early- stage dementia of the Alzheimer's type. *Psychology and Aging*, 20, 33–46.

Brikenkamp, R. (1981). *Test d2.Aufmerksamkeits-Belastungs-Test*.Verlag fur Psychologie Hogrefe, Goettingen-Toronto-Zurich.

Brown, W.S., Marsh, J.T., & LaRue, A. (1983). Exponential electrophysiological aging: P3 latency. *Electroencephalography and clinical Neurophysiology*, *55(3),* 277–285.

Buchner, A., & Mayr, S. (2004). Auditory negative priming in younger and older adults. *The Quarterly Journal of Experimental Psychology*, *57A*, 769–787.

Bunting, M. (2006). Proactive interference and item similarity in working memory. *Journal of Experimental Psychology: Learning, Memory, and Cognition, 32,* 183–196.

Burgess, P. W., & Shallice, T. (1997). The relationship between prospective and retrospective

memory: Neuropsychological evidence. in M. A. Conway (ed.), Cognitive models of memory (pp. 247–272). Cambridge, Ma: Mit Press.

Burgess, P. W., Dumontheil,I., Gilbert, S., Okuda,J., Schölvinck, M., & Simons, J. (2008). On the role of rostral prefrontal cortex (area 10) in prospective memory. In M. Kliegel, M. A. McDaniel, & G. O. Einstein (Eds.), *Prospective memory: Cognitive, neuroscience, developmental, and applied perspective*s. Mahwah: Erlbaum.

Burgess, P.W., Gonen-Yaacovi, G., & Volle, E. (2011). Functional neuroimaging studies of prospective memory: What have we learnt so far? *Neuropsychologia*, *49*, 2246–2257.

Burton, C.L., Hultsch, D.F., Strauss, E., & Hunter, M.A. (2002). Intraindividual variability in physical and emotional functioning: comparison of adults with traumatic brain injuries and healthy adults. *Clinical Neuropsychology*, *16*, 264–279.

Bustamante J, Rimola A, Ventura PJ, Navasa M, Cirera I, Reggiardo V, et al. (1999) Prognostic significance of hepatic encephalopathy in patients with cirrhosis. *Journal of Hepatology*, 30, 890–895.

Butler, K. M., Zacks, R. T., & Henderson, J. M. (1999). Suppression of reflexive saccades in younger and older adults: Age comparisons on an antisaccade task. *Memory & Cognition*, *27*, 584–591.

Butterworth RF. (1996). The neurobiology of hepatic encephalopathy. *Seminars in Liver Diseases, 16*, 235–244.

Butterworth, R. F. (2000). Complications of cirrhosis III. Hepatic encephalopathy. *Journal of Hepatology*, *32*(1 Suppl), 171– 80.

Cabeza, R. (2002) Hemispheric asymmetry reduction in old adults: the HAROLD model. *Psychology of Aging*. 17, 85–100.

Cabeza, R., Anderson, N. D., Locantore, J. K., & McIntosh, A. R. (2002). Aging gracefully: Compensatory brain activity in high-performing older adults. *NeuroImage, 17*(3), 1394-1402.

Cabeza, R., Daselaar, S. M., Dolcos, F., Prince, S. E., Budde, M., & Nyberg, L. (2004). Task-

independent and task-specific age effects on brain activity during working memory, visual attention and episodic retrieval. *Cerebral Cortex*, *14*(4), 364–375.

Cabeza, R., Grady, C. L., Nyberg, L., McIntosh, A. R., Tulving, E., Kapur, S., et al. (1997). Age-related differences in neural activity during memory encoding and retrieval: A positron emission tomography study. *Journal of Neuroscience, 17(1),* 391–400.

Carlson, M. C., Hasher, L., Connelly, S. L., & Zacks, R. T. (1995). Aging, distraction, and the benefits of predictable location. *Psychology and Aging*, *10*, 427–436.

Casellas, F., Sagalés, T., de la Calzada, M.D., Accarino, A., Vargas, V., & Guarner, L. (1985). Visual evoked potentials in hepatic encephalopathy. *Lancet, 325,* 394–395.

Castellanos, F.X., Sonuga-Barke, E.J., Milham, M.P., & Tannock, R. (2006). Characterizing cognition in ADHD: beyond executive dysfunction. *Trends in Cognitive Science, 10,* 117–123.

Castellanos, F.X., Sonuga-Barke, E.J., Scheres, A., Di, M.A., Hyde, C., & Walters, J.R. (2005). Varieties of attention-deficit/hyperactivity disorder-related intra-individual variability. *Biological Psychiatry*, *57*, 1416–1423.

Cerella, J. (1985). Information processing rates in the elderly. *Psychological Bulletin*, *1,* 67–83.

Chambers, C. D., Garavan, H., & Bellgrove, M. A. (2009). Neuroscience and Biobehavioral Reviews: Insights into the neural basis of response inhibition from cognitive and clinical neuroscience. *Biobehavioral Reviews*, *33*, 631–646.

Chambers, C.D., Bellgrove, M.A., Stokes, M.G., Henderson, T.R., Garavan, H., Robertson, I.H., Morris, A.P., & Mattingley, J.B. (2006). Executive 'brake failure' following deactivation of human frontal lobe. *Journal of Cognitive Neuroscience, 18,* 444– 455.

Chen, Y., Huang, X., Jackson, T., & Yang, H. (2009). Effect of characteristics of target cues on task interference from prospective memory. *NeuroReport*, 20, 81–86.

Chen, Y., Huang, X., Ren, G., Chen, Y., & Yue, C. (2007). Task interference from event-based prospective memory : an event-related potentials study, *NeuroReport*, *18*, 1951–1955.

Cherry, K. E., & Le Compte, D. C. (1999). Age and individual differences influence prospective memory. *Psychology and Aging*, *14*, 60–76.

Cherry, K. E., Martin, R. C., Simmons-D'Gerolamo, S. S., Pinkston, J. B., Griffing, A., & Gouvier, W. D. (2001). Prospective remembering in younger and older adults: role of the prospective cue. *Memory, 9,* 177–193.

Cherry, K.E., & Park, D.C. (1993).Individual differenced and contextual variables influence spatial memory in younger and older adults. *Psychology and Aging*, *8*, 517–526.

Chiappe, P., Hasher, L., & Siegel, L. S. (2000). Working memory, inhibitory control, and reading disability. *Memory & Cognition, 28,* 8–17.

Christensen, H., Dear, K.B., Anstey, K.J., Parslow, R.A., Sachdev, P., & Jorm, A.F. (2005). Within- occasion intraindividual variability and preclinical diagnostic status: is intraindividual variability an indicator of mild cognitive impairment? *Neuropsychology*, *19*, 309–317.

Chu, N.S., & Yang, S.S. (1988). Portal-systemic encephalopathy: Alterations in somatosensory and brainstem auditory evoked potentials. *Journal of the Neurological Sciences, 84,* 41–50.

Chu, N.S., Yang, S.S., & Liaw, Y.F. (1997). Evoked potentials in liver diseases. *Journal of Gastroenterology and Hepatology, 12,* S288–S293.

Ciancio, A., Marchet, A., Saracco, G., Carucci, P., Lavezzo, B., Leotta, D., Capellero, B., Nobili, M., Smedile, A., & Rizzetto, M. (2002). Spectral electroencephalogram analysis in hepatic encephalopathy and liver transplantation. *Liver Transplantation journal, 8,* 630–635.

Cockburn, J., & Smith, P. T. (1988). Effects of age and intelligence on everyday memory tasks. In M. M. Gruneberg, P. E. Morris, & R. N. Sykes (Eds.), *Practical aspects of memory: Current research and issues. Vol. 2: Clinical and educational implications* (pp. 132-136). Chichester, U.K.: Wiley.

Cohen, A. L., West, R., & Craik, F. I. M. (2001). Modulation of the prospective and retrospective components of memory for intentions in younger and older adults. *Aging, Neuropsychology and Cognition, 8,* 1–13.

Cohen, J. D., Dunbar, K., & McClelland, J. L. (1990). On the control of automatic processes: A parallel distributed processing account of the Stroop effect. *Psychological Review, 97,* 332–361.

Cohen, J.D., Braver, T.S., O'Reilly, R. (1996). A computational approach to prefrontal cortex, cognitive control, and schizophrenia: recent developments and current challenges. *Philosophical Transactions of the Royal Society B: Biological Sciences*, *351*, 1515–1527.

Collette, F., Germain, S., Hogge, M., & Van der Linden, M. (2009). Inhibitory control of memory in normal ageing: dissociation between impaired intentional and preserved unintentional processes. *Memory*, *17*(1), 104–22.

Cona, G., Arcara, G., Tarantino V., & Bisiacchi, P.S (in press). Electrophysiological correlates of strategic monitoring in event-based and time-based prospective memory. *PLoSONE*.

Conn, H.O., Leevy, C.M., Vlahcevic, Z.R., Rodgers, J.B., Maddrey, W.C., Seeff, L., & Levy, L.L. (1977). Comparison of lactulose and neomycin in the treatment of chronic portal-systemic encephalopathy. A double blind controlled trial. *Gastroenterology, 72*, 573–583.

Connelly, S. L., & Hasher, L. (1993). Aging and the inhibition of spatial location. *Journal of Experimental Psychology: Human Perception and Performance*, 19, 1238–1250.

Costa, A., Oliveri, M., Barban, F., Torriero, S., Salerno, S., Lo Gerfo, E., Koch, G., et al. (2011). Keeping Memory for Intentions: A cTBS Investigation of the Frontopolar Cortex. *Cerebral cortex*, 1-8.

Cowan, N. (1995). *Attention and memory: An integrated framework*. Oxford University Press: New York.

Cowan, N. (1999). An embedded-processes model of working memory. In: Miyake, A., Shah, P. (Eds.), *Models of working memory: mechanisms of active maintenance and executive control.* Cambridge University Press, Cambridge, pp. 62–101.

Cowan, N. (2001) The magical number 4 in short-term memory: A reconsideration of mental storage capacity. *Behavioural Brain Science, 24,* 87–185

Craik, F. I. M. (1983). On the transfer of information from temporary to permanent memory. *Philosophical Transactions of the Royal Society, London, Series B*, 302, 341–359.

Craik, F. I. M., & Bosman, E. A. (1992). Age-related changes in memory and learning. In H. Bouma & J. Graafmans (Eds.), *Gerontechnology: Proceedings of the First International Conference on Technology and Aging* (pp. 79–92). Eindhoven: IOS Press

Craik, F. I. M., & Byrd, M. (1982). Aging and cognitive deficits: The role of attentional resources. In F. I. M. Craik & S. Trehub (Eds.), *Aging & Cognitive Processes: Advances in the Study of Communication and Affect* (Vol. 8, pp. 191-211). New York: Plenum Press.

Craik, F.I.M. (1986). A functional account of age differences in memory. In: F. Clix & H. Hangendorf (eds.) *Human Memory and Cognitive Capabilities: Mechanisms and Performances*, pp. 409–422. Amsterdam: Elsevier.

D'Avanzo, C., Schiff, S., Amodio, P., & Sparacino, G. (2011). A Bayesian method to estimate single- trial event-related potentials with application to the study of the P300 variability. *Journal of Neuroscience Method*. *198*, 114–124.

d'Ydewalle, G. (1995). Age-related interference of intervening activities in a prospective memory task. *Psychologica Belgica, 35,* 189–203.

d'Ydewalle, G., & Brunfaut, E. (1996). Are older subjects necessarily worse in prospective memory tasks? In M. Georgas, E. Manthouli, E. Besevegis, & A. Kokkevi (Eds.), *Contemporary psychology in Europe: Theory, research and applications* (pp. 161–172). Gottingen, Germany: Hogrefe & Huber.

d'Ydewalle, G., Bouckaert, D., & Brunfaut, E. (2001). Age-related differences and complexity of ongoing activities in time- and event-based prospective memory. *American Journal of Psychology, 114,* 411–423.

d'Ydewalle, G., Luwel, K., & Brunfaut, E. (1999). The importance of on-going concurrent activities as a function of age in time- and event- based prospective memory. *European Journal of Cognitive Psychology, 11,* 219–237.

Daffner, K. R., Chong, H., Sun, X., Tarbi, E. C., Riis, J. L., McGinnis, S. M., & Holcomb, P. J.

(2011). Mechanisms underlying age- and performance-related differences in working memory. *Journal of cognitive neuroscience*, *23*(6), 1298–314.

Daffner, K. R., Rentz, D., Scinto, L. F. M., Faust, R., Budson, A. E., & Holcomb, P. J. (2001). Pathophysiology underlying diminished attention to novel events in patients with early AD. *Neurology, 56,* 1377–1383.

Daffner, K. R., Ryan, K. K., Williams, D. M., Budson, A. E., Rentz, D. M., Wolk, D. A, & Holcomb, P. J. (2006). Increased responsiveness to novelty is associated with successful cognitive aging. *Journal of cognitive neuroscience*, *18(10),* 1759–73.

Daffner, K.R., Mesulam, M.M., Scinto, L.F.M., Cohen, L.G., Kennedy, B.P., West, W.C., & Holcomb, P.J. (1998). Regulation of attention to novel stimuli by frontal lobes: an event-related potential study. *NeuroReport, 9,* 787–791.

Damoiseaux, J. S., Beckmann, C. F., Arigita, E., Barkhof, F., Scheltens, P., Stam, C. J., & Rombouts, S. B. (2008). Reduced resting-state brain activity in the "default network" in normal aging. *Cerebral Cortex*, *18*, 1856–1864.

Daselaar, S. M., & Cabeza, R. (2005). Age-related changes in hemispheric organization. In R. Cabeza, L. Nyberg, & D. Park (Eds.), *Cognitive neuroscience of aging* (pp. 325–353). Oxford: Oxford University Press.

Davis, S. W., Dennis, N. A., Daselaar, S. M., Fleck, M. S., & Cabeza, R. (2007). Que PASA? The posterior anterior shift in aging. *Cerebral Cortex, 18,* 1201–1209.

De Beni, R., & Palladino, P. (2004). Decline in working memory updating through ageing: Intrusion error analyses. *Memory, 12,* 75–89.

De Frias, C. M., Dixon, R. A., & Strauss, E. (2009). Characterizing executive functioning in older special populations: From cognitively elite to cognitively impaired. *Neuropsychology, 23,* 778–791.

De Frias, C. M., Dixon, R. F., & Strauss, E. (2006). Structure of four executive functioning tests in healthy older adults. *Neuropsychology, 20,* 206–214.

De Jong, R., Liang, C.C., & Lauber, E. (1994). Conditional and unconditional automaticity: a dual- process model of effects of spatial stimulus-response correspondence. *Journal of Experimental Psychology*, 20, 731–750.

De Jong, R., Wierda, M., Mulder, G., & Mulder, L.J.M., (1988). Use of partial stimulus information in response processing. *Journal of Experimental Psychology, 14,* 682–692.

De Lucia, M., Michel, C.M., & Murray, M.M. (2010) Comparing ICA-based and Single-Trial Topographic ERP Analyses. *Brain Topography*, *23*, 119–127.

Delorme, A., & Makeig, S. (2004) EEGLAB: an open source toolbox for analysis of single-trial EEG dynamics including independent component analysis. *Journal of Neuroscience Methods*, *134*, 9–21.

Dempster, F.N. (1991). Inhibitory processes: a neglected dimension of intelligence. *Intelligence*, *15*, 157–73.

Development Core Team (2011). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. ISBN 3-900051-07-0, http://www.R-project.org

Devolder, P. A., Brigham, M. C., & Pressley, M. (1990). Memory performance awareness in younger and older adults. *Psychology and Aging, 5,* 291–303.

Dhiman RK, & Chawla YK. (2009). Minimal hepatic encephalopathy. *Indian Journal of Gastroenterology, 28,* 5–16.

Dillon, D.G., & Pizzagalli, D.A. (2007). Inhibition of action, thought, and emotion: a selective neurobiological review. *Applied and Preventive Psychology*, *12*, 99–114.

Dimoska, A., Johnstone, S.J., Barry, R.J., & Clarke, A. (2003). Inhibitory motor control in children with Attention-deficit/Hyperactivity Disorder: Event-related potentials in the stop-signal paradigm. *Biological Psychiatry, 54,* 1340–1349.

Dobbs, A.R., & Rule, B.G. (1987). Prospective memory and self-reports of memory abilities in older adults. *Canadian Journal of Psychology, 41,* 209–222.

Donchin, E., & Coles, M. G. (1988). Is the P300 component a manifestation of context updating? *Behavioral and Brain Sciences, 11,* 357–427.

Donkers, F.C.L., & Van Boxtel, G.J.M., (2004). The N2 in go/nogo tasks reflects conflict monitoring not response inhibition. *Brain Cognition*, *56*, 165–176.

Duarte, A., Ranganath, C., Trujillo, C., & Knight, R.T. (2006). Intact recollection memory in high-performing older adults: ERP and behavioral evidence. *Journal of Cognitive Neuroscience*, *18*, 33–47.

Eimer M. (1996). The N2pc component as an indicator of attentional selectivity. *Electroencephalography and Clinical Neurophysiology 99,* 225–34.

Eimer, M. (1993). Effects of attention and stimulus probability on ERPs in a go/no-go task. *Biological Psychology, 35,* 123–138.

Eimer, M., & Schlaghecken, F. (1998). Effects of masked stimuli on motor activation: behavioral and electrophysiological evidence. *Journal of Experimental Psychology: Human Perception and Performance, 24,* 1737–1747.

Einstein, G. O., & McDaniel, M. A. (1990). Normal aging and prospective memory. *Journal of Experimental Psychology: Learning, Memory, and Cognition*, *16*, 717–726.

Einstein, G. O., & McDaniel, M. A. (1996). Retrieval processes in prospective memory: Theoretical approaches and some new empirical findings. In M. Brandimonte, G. O. Einstein, & M. A. McDaniel (Eds.), *Prospective memory: Theory and applications* (pp. 115–142). Hillsdale, NJ: Erlbaum.

Einstein, G. O., Holland, L. J., McDaniel, M. A., & Guynn, M. J. (1992). Age-related deficits in prospective memory: The influence of task complexity. *Psychology and Aging, 7,* 471–478.

Einstein, G. O., McDaniel, M. A., Manzi, M., Cochran, B., & Baker, M. (2000). Prospective Memory and Aging: Forgetting Intentions Over Short Delays. *Psychology and Aging, 15(4),* 1–13.

Einstein, G. O., McDaniel, M. A., Richardson, S. L., Guynn, M. J., & Cunfer, A. R. (1995). Aging and prospective memory: Examining the influences of self-initiated retrieval processes. *Journal of Experimental Psychology: Learning, Memory, and Cognition, 21,* 996–1007.

Ellis, J. (1996). Prospective memory or the realization of delayed intentions: A conceptual framework for research. In M. Brandimonte, G. O. Einstein, & M. A. McDaniel (Eds.), *Prospective memory: Theory and applications* (pp. 1–22). Mahwah, NJ: Erlbaum.

Ellis, J., & Milne, A. (1996). Retrieval cue specificity and the realization of delayed intentions. *Quarterly Journal of Experimental Psychology, 49,* 862–887.

Ellis, J., Kvavilashvili, L., & Milne, A. (1999). Experimental tests of prospective remembering: The influence of cue-event frequency on performance. *British Journal of Psychology, 90,* 9–23.

Elsass, P., Christensen, S.E., Mortensen, E.L., & Vilstrup, H. (1985). Discrimination between organic and hepatic encephalopathy by means of continuous reaction times. *Liver, 5,* 29–34.

Elsass, P., Lund, Y., & Ranek, L. (1978). Encephalopathy in patients with cirrhosis of the liver. A neuropsychological study. *Scandinavian Journal of Gastroenterology, 13,* 241–247.

Eppinger, B., Kray, J., Mecklinger, A., & John, O. (2007). Age difference in task switching and response monitoring: Evidence from ERPs. *Biological Psychology, 75,* 52–67.

Eriksen, B. A., & Eriksen, C. W. (1974). Effects of noise letters upon the identification of a target letter in a nonsearch task. *Perception & Psychophysics, 16,* 143–149.

Escera, C., Alho, K., Schröger, E., & Winkler, I., (2000). Involuntary attention and distractibility as evaluated with event-related brain potentials. *Audiology and Neurootology, 5,* 151–166.

Escera, C., Yago, E., & Alho, K. (2001). Electrical responses reveal the temporal dynamics of brain events during involuntary attention switching. *European Journal of Neuroscience, 14*, 877–883.

Falkenstein, M., Hoormann, J., & Hohnsbein, J. (1999). ERP components in go/nogo tasks and their relation to inhibition. *Acta Psychologica*, *101*, 267–291.

Falkenstein, M., Hoormann, J., & Hohnsbein, J. (2001). Changes of error- related ERPs with age. *Experimental Brain Research, 138,* 258–262.

Falkenstein, M., Hoormann, J., & Hohnsbein, J. (2002). Inhibition-related ERP components: Variation with modality, age, and time-on-task. *Journal of Psychophysiology, 16(3),* 167–175.

Falkenstein,M., Koshlykova, N. A., Kiroj, V. N., Hoormann, J., & Hohnsbein, J. (1995). Late ERP components in visual and auditory go/nogo tasks. *Electroencephalography and Clinical Neurophysiology*, *96*, 36–43.

Fallgatter, A. J., Mueller, T. J., & Strik,W. K. (1999). Age-related changes in the brain electrical correlates of response control. *Clinical Neurophysiology, 110,* 833–838.

Fassbender, C., Zhang, H., Buzy, W.M., Cortes, C.R., Mizuiri, D., Beckett, L., & Schweitzer, J.B. (2009). A lack of default network suppression is linked to increased distractibility in ADHD. *Brain Research*, *1273*, 114–128.

Fein, G., & Turetsky, B. (1989). P300 latency variability in normal elderly: Effects of paradigm and measurement technique. *Electroencephalography and Clinical Neurophysiology, 72,* 384–394.

Felipo, V., Ordoño, J.F., Urios, A., Mlili, N.E., Giménez- Garzó, C., Aguado, C., … Montoliu, C. (in press). Patients with minimal hepatic encephalopathy show impaired mismatch negativity correlating with reduced performance in attention tests. *Hepatology.* DOI: 10.1002/hep.24704.

Fell, J. (2007). Cognitive neurophysiology: beyond averaging. *Neuroimage, 37*, 1069–1072.

Ferenci,P., Lockwood, A., Mullen, K.,Tarter,R.,Weissenborn, K., & Blei, A.T. (2002).Hepatic encephalopathy– definition, nomenclature, diagnosis, and quantification: Final report of the working party at the 11th World Congresses of Gastroenterology, Vienna, 1998. *Hepatology, 35,* 716–721.

Fernandez-Duque, D., & Black, S. E. (2006). Attentional networks in normal aging and Alzheimer's disease. *Neuropsychology*, *20*, 133–143.

Fisk, J.E., & Sharp, C.A. (2004). Age-related impairment in executive functioning: Updating, inhibition, shifting, and access. *Journal of Clinical and Experimental Neuropsychology*, *26*, 874–890.

Fjell, A. M., & Walhovd, K. B. (2001). P300 and neuropsychological tests as measures of aging: Scalp topography and cognitive changes. *Brain Topography,* 14, 25–40.

Fjell, A.M., Rosquist, H., & Walhovd, K.B. (2009). Instability in the latency of P3a/P3b brain potentials and cognitive function in aging. *Neurobiology of Aging*, *30*, 2065–2079.

Fogelson, N., Shah, M., Bonnet-Brilhault, F., & Knight, R. (2010). Electrophysiological evidence for aging effects on local contextual processing, *Cortex*, *46*(4), 498–506.

Folstein, F., Folstein, S.E., & McHugh, P.R. (1975). "Mini-mental state": A practical method for grading the cognitive state of patients for the clinician, *Journal of Psychiatric Research*, 12(3), 189–198.

Folstein, J. R., & Van Petten, C. (2008). Influence of cognitive control and mismatch on the N2 component of the ERP: a review. *Psychophysiology*, *45*(1), 152–70.

Forstmann, B.U., van den Wildenberg, W.P.M., & Ridderinkhof, K.R. (2008). Neural Mechanisms, Temporal Dynamics, and Individual Differences in Interference Control. *Journal of Cognitive Neuroscience, 20,* 1854–1865.

Friedman, D. & Simpson, G. (1994). Amplitude and scalp distribution of target and novel events: effects of temporal order in young, middle-aged and older adults. *Cognitive Brain Research*, 2, 49–63.

Friedman, D., Cycowicz, Y.M., & Gaeta, H., (2001). The novelty P3: an event- related brain potential (ERP) sign of the brain's evaluation of novelty. *Neuroscience Biobehavioural Review*. 25, 355–373

Friedman, D., Nessler, D., Johnson, R., Ritter, W., & Bersick, M. (2008). Age-related changes in executive function: an event- related potential (ERP) investigation of task-switching. *Neuropsychology, development, and cognition, Section B: Aging, 15*, 95–128.

Friedman, N. P., & Miyake, A. (2004). The relations among inhibition and interference control functions: A latent-variable analysis. *Journal of Experimental Psychology: General*, *133*, 101–135.

Fristoe, N. M., Salthouse, T. A., & Woodward, J. L. (1997). Examination of age-related deficits on the Wisconsin Card Sorting Test. *Neuropsychology, 11,* 428–436.

Funke, J., & Krüger, T. (1993). Plan-A-Day (PAD). Bonn, Germany: Psychologisches institut der Universität Bonn.

Gallai,V.,Alberti, A., Balò, S., Mazzotta, G., Clerici, C.,Gentili, G., Firenze, C., & Morelli, A. (1995). Cognitive event-related potential in hepatic encephalopathy. *Acta Neurologica Scandinavica, 91,* 358–361.

Garavan, H. (1998). Serial attention within working memory. *Memory and Cognition, 26,* 263–276.

Garavan, H., Ross, T. J., & Stein, E. A. (1999). Right hemispheric dominance of inhibitory control: An event-related functional MRI study. *Proceedings of the National Academy of Sciences, U.S.A., 96,* 8301–8306.

Gazzaley, A., Cooney, J. W., Rissman, J., & D'Esposito, M. (2005). Top-down suppression deficit underlies working memory impairment in normal aging. *Nature Neuroscience*, *8(10),* 1298–1300.

Geisser, S., & Greenhouse, S. (1959) On methods in the analysis of profile data. *Psychometrika*, *24*, 95–112.

Gilberstadt, S.J., Gilberstadt, H., Zieve, L., Buegel, B., Collier, R.O., Jr., & McClain, C.J. (1980). Psychomotor performance defects in cirrhotic patients without overt encephalopathy. *Archives of Internal Medicine*, *140*, 519–521.

Gilbert, S.J., Gollwitzer, P.M., Cohen, A.L., Burgess, P.W., & Oettingen, G. (2009). Separable brain systems supporting cued versus self-initiated realization of delayed intentions. *Journal of Experimental Psychology: Learning, Memory, and Cognition, 35,* 905–915.

Gleckman, R.A. (1992). Urinary tract infection. *Clinic in Geriatric Medicine,* 8, 793–803.

Grady, C. L., Bernstein, L. J., Beig, S., & Siegenthaler, A. L. (2002). The effects of encoding task on age-related differences in the functional neuroanatomy of face memory. *Psychology and Aging, 17(1),* 7–23.

Grady, C. L., Haxby, J. V., Horwitz, B., Schapiro, M. B., Rapoport, S., Ungerleider, L. G., & Herscovitch, P. (1992). Dissociation of object and spatial vision in human extrastriate cortex: Age- related changes in activation of regional cerebral blood flow measured with [15O] water and positron emission tomography. *Journal of Cognitive Neuroscience, 4*, 23–34.

Grady, C. L., Maisog, J. M., Horwitz, B., Ungerleider, L. G., Mentis, M. J., Salerno, J. A., et al. (1994). Age-related changes in cortical blood flow activation during visual processing of faces and location. *Journal of Neuroscience, 14(3, Pt 2),* 1450–1462.

Grady, C. L., McIntosh, A. R., Bookstein, F., Horwitz, B., Rapoport, S. I., & Haxby, J. V. (1998). Age-related changes in regional cerebral blood flow during working memory for faces. *Neuroimage, 8(4),* 409–425.

Grady, C. L., McIntosh, A. R., Horwitz, B., Maisog, J. M., Ungerleider, L. G., Mentis, M. J., et al. (1995). Age-related reductions in human recognition memory due to impaired encoding. *Science, 269 (5221),* 218–221.

Gratton, G., Coles, M. G. H., Sirevaag, E. J., Eriksen, C. W., & Donchin, E. (1988). Pre- and poststimulus activation of response channels: A psychophysiological analysis. *Journal of Experimental Psychology: Human Perception and Performance, 14,* 331-344.

Gratton, G., Coles, M.G.H., Sirevaag, E.J., Eriksen, C.W., & Donchin, E. (1988). Pre- and post-stimulus activation of response channels: A psychophysiological analysis. *Journal of Experimental Psychology: Human Perception and Performance*,14, 331–344.

Groeneweg, M., Quero, J.C., De Bruijn, I., Hartmann, I.J., Essink-bot,M.L., Hop,W.C., & Schalm, S.W. (1998). Subclinical hepatic encephalopathy impairs daily functioning. *Hepatology, 28,* 45–49.

Guerit, J.M., Amantini, A., Fischer, C., Kaplan, P. W., Mecarelli, O., & Schnitzler, A. (2009).

Neurophysiological investigations of hepatic encephalopathy : ISHEN practice guidelines. *Liver International*, 789–796.

Guerreiro, M. J. S., Murphy, D. R., & Van Gerven, P. W. M. (2010). The role of sensory modality in age-related distraction: a critical review and a renewed view. *Psychological bulletin*, *136*(6), 975-1022.

Gunning-Dixon, F. M., & Raz, N. (2000). The cognitive correlates of white matter abnormalities in normal aging: A quantitative review. *Neuropsychology, 14(2),* 224–232.

Guynn, M.J. (2003). A two-process model of monitoring in event-based prospective memory: Activation/retrieval mode and checking. *International Journal of Psychology, 38*, 245–256.

Guynn, M.J. (2008). Theory of monitoring in prospective memory: Instantiating a retrieval mode and periodic target checking. In: Kliegel M, McDaniel MA, Einstein GO, eds. *Prospective memory: Cognitive, neuroscience, developmental, and applied perspectives*. (pp 53–76). New York: Lawrence Erlbaum Associates.

Guynn, M.J., McDaniel, M.A., & Einstein, G.O. (2001). Remembering to perform intentions: A different type of memory? In: Zimmer H.D., Cohen R.L., Guynn M.J., Engelkamp J., Kormi-Nouri R., and Foley M.A. (eds.) *Memory for Action: A Distinct Form of Episodic Memory?* (pp. 25–48). Oxford: Oxford University Press.

Hallett, P. E. (1978). Primary and secondary saccades to goals defined by instructions. *Vision Research, 18,* 1279–1296.

Hambrick, D.Z., Helder, E. A., Hasher, L., Zacks, R. T., & Swensen, E. (2005). The relationship between inhibition and working memory: A latent-variable approach. *Paper presented at the annual meeting of the Psychonomic Society*, Toronto, Ontario, Canada.

Harnishfeger, K. (1995). The development of cognitive inhibition. Theories, definitions, and research evidence. In F. N. Dempster & C. J. Brainerd (Eds.), *Interference and inhibition in cognition* (pp. 176–206). London: Academic Press.

Harris, J. E. & Wilkins, A. J. (1982). Remembering to do things: A theoretical framework and an illustrative experiment. *Human Learning*, *1*, 123–136.

Hartman, M., Dumas, J., & Nielsen, C. (2001). Age differences in updating working memory: Evidence from the delayed-matching-to-sample test. *Aging, Neuropsychology, and Cognition, 8*, 14–35.

Hasher, L., & Zacks, R. T. (1988). Working memory, comprehension, and aging: A review and a new view. In G. H. Bower (Ed.), *The Psychology of Learning and Motivation* (Vol. 22, pp. 193–225). New York: Academic Press.

Hasher, L., & Zacks, R.T. (1979). Automatic and effortful processes in memory. *Journal of Experimental Psychology: General*, *108*, 356–388.

Hasher, L., Zacks, R. T., & May, C. P. (1999). Inhibitory control, circadian arousal, and age. In D. Gopher & A. Koriat (Eds.), *Attention and performance XVII, Cognitive regulation of performance. Interaction of theory and application* (pp. 653–675). Cambridge, MA: The MIT Press.

Heaton, R. K., Chelune, G. J., Talley, J. L., Kay, G.G, & Curtis, G. (1993). Wisconsin Card Sorting Test manual: Revised and expanded. Odessa, FL: Psychological Assessment Resources.

Hedden, T., & Gabrieli, J. D. E. (2004). Insights into the ageing mind: a view from cognitive neuroscience. *Nature reviews. Neuroscience*, *5(2),* 87-96.

Hedden, T., & Park, D. C. (2003). Contributions of source and inhibitory mechanisms to age-related retroactive interference in verbal working memory. *Journal of Experimental Psychology: General, 132,* 93–112.

Hedden, T., & Park, D.C. (2001). Aging and interference in verbal working memory. *Psychology of Aging*,*16*, 666.

Hedden, T., & Yoon, C. (2006). Individual differences in executive processing predict susceptibility to interference in verbal working memory. *Neuropsychology, 20,* 511–528.

Henry, J. D., MacLeod, M. S., Phillips, L. H., & Crawford, J. R. (2004). A meta-analytic review of prospective memory and aging. *Psychology and Aging*, *19*, 27–39.

Hertzog, C., Park, D., Morell, R. W., & Martin, M. (2000). Behavioural specificity in the accuracy of subjective memory complaints. *Applied Cognitive Psychology, 14,* 257–275.

Hicks, J. L., Marsh, R. L., & Cook, G. I. (2005). Memory and Language Task interference in time-based, event-based, and dual intention prospective memory conditions. *Journal of Memory and Language*, *53*, 430–444.

Hillman, C. H., Kramer, A. F., Belopolsky, A. V., & Smith, D. P. (2006). A cross-sectional examination of age and physical activity on performance and event-related brain potentials in a task switching paradigm. *International Journal of Psychophysiology, 59(1),* 30–39.

Hitch, G.J., & Ferguson, J. (1991). Prospective memory for future intentions: some comparisons with memory for past events, *European Journal of Cognitive Psychology, 3(3),* 285–295.

Hölig, C., & Berti, S. (2010). To switch or not to switch: brain potential indices of attentional control after task-relevant and task-irrelevant changes of stimulus features. *Brain research*, *1345*, 164–75.

Horváth, J., Czigler, I., Birkás, E., Winkler, I., & Gervai, J. (2009). Age-related differences in distraction and reorientation in an auditory task. *Neurobiology of aging*, *30*(7), 1157–72.

Houx, P. J., Jolles, J., & Vreeling, F. W. (1993). Stroop interference: Aging effects assessed with the Stroop Color-Word Test. *Experimental Aging Research*, 19(3), 209–224.

Hu, L., Mouraux, A., Hu, Y., & Iannetti, G.D. (2010). A novel approach for enhancing the signal-to- noise ratio and detecting automatically event-related potentials (ERPs) in single trials. *Neuroimage*, *50*, 99–111.

Hultsch, D.F., MacDonald, S.W., & Dixon, R.A. (2002). Variability in reaction time performance of younger and older adults. *Journal of Gerontology Biology Psychology Science, 57*, 101–115.

Hultsch, D.F., MacDonald, S.W., Hunter, M.A., Levy-Bencheton, J., & Strauss, E. (2000). Intraindividual variability in cognitive performance in older adults: comparison of adults with mild dementia, adults with arthritis, and healthy adults. *Neuropsychology*, *14*, 588–598.

Huynh, H., & Feldt, L. S. (1976). Estimation of the Box correction for degrees of freedom from sample data in randomized block and split-plot designs. *Journal of Educational Statistics,* 1, 69–82.

Insel, K., Morrow, D., Brewer, B., & Figueredo, A. (2006). Executive function,working memory, and medication adherence among older adults. *Journal of Gerontology: Psychological Sciences*, *61B*, P102–P107.

Jäger, T., & Kliegel, M. (2008). Time-based and event-based prospective memory across adulthood: Underlying mechanisms and differential costs on the ongoing task. *Journal of General Psychology, 135,* 4–22

Jalan R, & Bernuau J. (2007). Induction of cerebral hyperemia by ammonia plus endotoxin: does hyperammonemia unlock the blood-brain barrier? *Journal of Hepatology, 47,* 168–171.

Jaskowski, P., & Verleger, R. (2000). An evaluation of methods for single-trial estimation of P3 latency. *Psychophysiology*, 37, 153–162.

Jennings, J. M., & Jacoby, L. L. (1993). Automatic versus intentional uses of memory: Aging, attention, and control. *Psychology and Aging, 8(2),* 283–293.

Joebges, E.M., Heidemann, M., Schimke, N., Hecker, H., Ennen, J.C., & Weissenborn, K. (2003). Bradykinesia in minimal hepatic encephalopathy is due to disturbances in movement initiation. *Journal of Hepatology*, *38*, 273– 280.

Johnson R, & Donchin E. (1982). Sequential expectancies and decision-making in a changing environment: an electrophysiological approach. *Psychophysiology, 19,* 183–200.

Jonides, J., Marshuetz, C., Smith, E., Reuter-Lorenz, P. A., Keoppe, R., & Hartley, A. (2000). Age differences in behavior and PET activation reveal differences in interference resolution in verbal working memory. *Journal of Cognitive Neuroscience, 12,* 188–196.

Joyce, C. A., Gorodnitsky, I. F., & Kutas, M. (2004). Automatic removal of eye movement and blink artifacts from EEG data using blind component separation. *Psychophysiology, 41,* 313–325.

Jung, T. P., Makeig, S., Humphries, C., Lee, T. W., McKeown, M. J., Iragui, V., & Sejnowski, T. J. (2000). Removing electroencephalographic artifacts by blind source separation. *Psychophysiology,* 37, 163–178.

Kaiser, S., Roth, A., Rentrop, M., Friederich, H.C., Bender, S., & Weisbrod, M. (2008). Intra-individual reaction time variability in schizophrenia, depression and borderline personality disorder. *Brain and Cognition*, *66*, 73-82.

Kane, M. J., & Engle, R. W. (2000). Working-memory capacity, proactive interference, and divided attention: Limits on long-term memory retrieval. *Journal of Experimental Psychology: Learning, Memory, and Cognition, 26,* 336–358.

Kane, M. J., May, C. P., Hasher, L., Rahhal, T., & Stoltzfus, E. R. (1997). Dual mechanisms of negative priming. *Journal of Experimental Psychology: Human Perception and Performance, 23,* 632–650.

Kelly, A.M., Uddin, L.Q., Biswal, B.B., Castellanos, F.X., & Milham, M.P. (2008). Competition between functional brain networks mediates behavioral variability. *Neuroimage*, 39, 527–537.

Kennedy, K. M., & Raz, N. (2009). Aging white matter and cognition: Differential effects of regional variations in diffusion properties on memory, executive functions, and speed. *Neuropsychologia, 47,* 916–927.

Khan, A., Sharma, N. K., & Dixit, S. (2008). Cognitive Load and Task Condition in Event- and Time-Based Prospective Memory : An Experimental Investigation. *Technology*, *142*(5), 517–531.

Kidder, D. P., Park, D. C., Hertzog, C., & Morrell, R. W. (1997). Prospective memory and aging: The effects of working memory and prospective memory task load. *Aging, Neuropsychology, and Cognition, 4,* 93–112.

Kieffaber, P. D., & Hetrick, W. P. (2005). Event-related potential correlates of task switching and switch costs. *Psychophysiology, 42(1),* 56–71.

Kircheis, G.,Wettstein,M., Timmermann, L., Schnitzler, A., & Haussinger, D. (2002). Critical

flicker frequency for quantification of low-grade hepatic encephalopathy. *Hepatology*, 35, 357–366.

Klein, C., Fischer, B., Hartnegg, K., Heiss, W.H., & Roth, M. (2000). Optomotor and neuropsychological performance in old age. *Experimental Brain Research, 135,* 141–154.

Kliegel, M., Jager, T., & Phillips, L. H. (2008). Adult Age Differences in Event-Based Prospective Memory : A Meta-Analysis on the Role of Focal Versus Nonfocal Cues. *Psychology and Aging*, *23*(1), 203–208.

Kliegel, M., Jäger, T., Altgassen, M., & Shum, D. (2008). Clinical neuropsychology of prospective memory. In M. Kliegel, M. A. McDaniel, & G. O. Einstein (Eds.), *Prospective memory* (pp. 283–308). NewYork: Erlbaum.

Kliegel, M., Martin, M., & Moor, C. (2003). Prospective memory and aging: Is task importance relevant? *International Journal of Psychology*, *38*, 207–214.

Kliegel, M., Martin, M., McDaniel, M. A., & Einstein, G. O (2002). Complex prospective memory and executive control of working memory: A process model. *Psychologische Beiträge, 44,* 303–318.

Kliegel, M., Ramuschkat, G., & Martin, M. (2003). Exekutive Funktionen und prospektive Gedär chtnisleistung im Alter: Eine differentielle Analyse von ereignis- und zeitbasierter prospektiver prospektive Gedächtnisleistung [Executive functions and prospective memory performance in old age: An analysis of event-based and time-based prospective memory]. *Zeitschrift für Gerontologie und Geriatrie, 36*, 35–41.

Knight, J. B., Ethridge, L. E., Marsh, R. L., & Clementz, B. A. (2010). Neural correlates of attentional and mnemonic processing in event-based prospective memory. *Frontiers in human neuroscience*, *4*, 5.

Kok, A. (1999). Varieties of inhibition: Manifestations in cognition, event- related potentials and aging. *Acta Psychologica, 101,* 129–158.

Kok, A. (2001). On the utility of P3 amplitude as a measure of processing capacity. *Psychophysiology, 38,* 557–577.

Kok, A., Ramautar, J.R., De Ruiter, M.B., Band, G.P., & Ridderinkhof, K.R. (2004). ERP components associated with successful and unsuccessful stopping in a stop-signal task. *Psychophysiology*, *41(1),* 9–20.

Konishi, S., Nakajima, K., Uchida, I., Kikyo, H., Kameyama, M., & Miyashita, Y. (1999). Common inhibitory mechanism in human inferior prefrontal cortex revealed by event-related functional MRI. *Brain, 122,* 981–991.

Kono, I., Ueda, Y., Nakajima, K., Araki, K., Kagawa, K., & Kashima, K. (1994). Subcortical impairment in subclinical hepatic encephalopathy. *Journal of the Neurological Sciences, 126,* 162–167.

Kopp, B., Mattler, U., Goertz, R., & Rist, F. (1996). N2, P3 and the lateralized readiness potential in a nogo task involving selective response priming. *Electroencephalography & Clinical Neurophysiology, 99,* 19–27.

Kramer, A.F., Humphrey, D.G., Larish, J.F., Logan, G.D., & Strayer, D.L. (1994). Aging and inhibition: Beyond a unitary view of inhibitory processing in attention. *Psychology and Aging*, *9*, 491–512.

Kramer, L., Bauer, E., Gendo, A., Funk, G., Madl, C., Pidlich, J., & Gangl, A. (2002). Neurophysiological evidence of cognitive impairment in patients without hepatic encephalopathy after transjugular intrahepatic portosystemic shunts. *American Journal of Gastroenterology, 97*,162–166.

Kray, J., & Lindenberger, U. (2000). Adult age differences in task switching. *Psychology and Aging, 15(1),* 126–147.

Kulisevsky, J., Conill, J., Avila, A., Pujol, J., Balanzo, J., & Capdevila, A. (1995). Abnormalities of the Bereitschaftspotential and MRI pallidal signal in non-encephalopathic cirrhotic patients. *Electroencephalography and Clinical Neurophysiology, 94,* 425–431.

Kullmann, F., Hollerbach, S., Holstege, A., & Scholmerich, J. (1995). Subclinical hepatic encephalopathy: The diagnostic value of evoked potentials *Journal of Hepatology,22,* 101–110.

Kutas, M., McCarthy, G., & Donchin, E. (1977). Augmenting mental chronometry: The P300 as a measure of stimulus evaluation time. *Science*, *197*, 792–795.

Kvavilashvili, L., & Ellis, J. (1996). Varieties of intentions: Some distinctions and classifications. In M. Brandimonte, G. O. Einstein, & M. A. McDaniel (Eds*.), Prospective memory: Theory and applications* (pp. 23–52). Mahwah, NJ: Erlbaum.

Kvavilashvili, L., & Fisher, L. (2007). Is time-based prospective remembering mediated by self-initiated rehearsals? Role of cues, ongoing activity, age and motivation. *Journal of Experimental Psychology: General*, *136*, 112–132.

Lamar, M., Yousem, D. M., & Resnick, S. M. (2004). Age differences in orbitofrontal activation: An fMRI investigation of delayed match and non-match to sample. *Neuroimage, 21(4),* 1368–1376.

Lawrence, M.A. (2011) ez: Easy analysis and visualization of factorial experiments. R package version 3.0-0. http://CRAN.R-project.org/package=ez

Li, S.C., & Lindenberger, U. (1999). Cross-level unification: a computational exploration of the link between deterioration of neurotransmitter systems and dedifferentiation of cognitive abilities in old age. In: Nilsson LG, Markowitsch H. *Cognitive neuroscience of memory*. (pp. 103–146). Berlin (Germany): Hogrefe and Huber.

Lindenberger, U., & Baltes, P. B. (1994). Sensory functioning and intelligence in old age: A strong connection. *Psychology and Aging, 9(3),* 339–355.

Liotti, M., Woldorff, M. G., Perez, R., & Mayberg, H. S. (2000). An ERP study of the temporal course of the Stroop color-word interference effect. *Neuropsychologia*, *38*, 701–711.

Liu, L. L., & Park, D. C. (2004). Aging and medical adherence: The use of automatic processes to achieve effortful things. *Psychology and Aging, 19,* 318–325.

Lizardi-cervera, J., Almeda, P., Guevara, L., & Uribe, M. (2003). Hepatic encephalopathy : A review. *Gastroenterology*, *2*(3).

Lobaugh, N. J., West, R., & McIntosh, A. R. (2001). Spatiotemporal analysis of experimental differences in event-related potential data with partial least squares. *Psychophysiology*, *38*(3), 517–530.

Lockwood, A.H., Murphy, B.W., Donnelly, K.Z., Mahl, T.C., & Perini, S. (1993). Positron-emission tomographic localization of abnormalities of brain metabolism in patients with minimal hepatic encephalopathy. *Hepatology, 18,* 1061–1068.

Lockwood, A.H., Yap, E.W.H., Rhoades, H.M., & Wong, W.-H. (1991). Altered cerebral blood flow and glucose metabolism in patients with liver disease and minimal encephalopathy. *Journal of Cerebral Blood Flow* and *Metabolism*, *11*, 331–336.

Logan, G. D., & Bundesen, C. (2003). Clever homunculus: Is there an endogenous act of control in the explicit task cuing procedure? *Journal of Experimental Psychology: Human Perception & Performance, 29,* 575–599.

Logan, G.D. (1994). On the Ability to Inhibit Thought and Action: A User's guide to the Stop Signal Paradigm. In: Dagenbach, D., Carr, T.H. (Eds.), *Inhibitory Processes in Attention, Memory, and Language*. (pp. 189–239). Academic Press, San Diego.

Logan, J. M., Sanders, A. L., Snyder, A. Z., Morris, J. C., & Buckner, R. L. (2002). Under-recruitment and nonselective recruitment: Dissociable neural mechanisms associated with aging. *Neuron, 33,* 827–840.

Logie, R. H., Maylor, E. A., Della Sala, S., & Smith, G. (2004). Working memory in event- and time-based prospective memory tasks: Effects of secondary demand and age. *The European Journal of Cognitive Psychology, 16,* 444– 456.

Luck, S. J., & Hillyard, S. A. (1994). Electrophysiological correlates of feature analysis during visual search. *Psychophysiology*, *31*, 291–308.

Lustig, C., Hasher, L., & Tonev, S. T. (2006). Distraction as a determinant of processing speed. *Psychonomic Bulletin & Review, 13,* 619–625.

Lustig, C., May, C. P., & Hasher, L. (2001). Working memory span and the role of proactive interference. *Journal of Experimental Psychology: General, 130,* 199–207.

Luszcz, M. A., & Lane, A. P. (2008). Executive function in cognitive neuropsychological, and clinical aging. In S. M. Hofer, & D. F. Alwin (Eds.), *Handbook of cognitive aging: Interdisciplinary perspectives.* London: Sage Publications.

MacDonald, S.W., Nyberg, & L., Backman, L. (2006). Intra-individual variability in behavior: links to brain structure, neurotransmission and neuronal activity. *Trends in Neuroscience*, *29*, 474–480.

Mack, A., & Rock, I. (1998). *Inattentional Blindness*. Cambridge, MA: MIT Press, 1998.

Magliero, A., Bashore, T.R., Coles, M.G., & Donchin, E. (1984). On the dependence of P300 latency on stimulus evaluation processes. *Psychophysiology*, *21,* 171–186.

Mäntylä, T., & Carelli, M. G. (2006). Time monitoring and executive functioning: Individual and developmental differences. In J. Glickson & M. Myslobodsky (Eds.), *Timing the future: The case for a time-based prospective memory* (pp. 191–211). New York: World Scientific.

Mäntylä, T., & Nilsson, L.G. (1997). Remembering to remember in adulthood: A population-based study of aging and prospective memory. *Aging, Neuropsychology, & Cognition, 4,* 81–92.

Mäntylä, T., Carelli, M. G., & Forman, H. (2007). Time monitoring and executive functioning in children and adults. *Journal of Experimental Child Psychology*, *96*, 1–19.

Mäntylä, T., Missier, F. D., & Nilsson, L.G. (2009). Age differences in multiple outcome measures of time-based prospective memory. *Neuropsychology, development, and cognition. Section B, Aging, neuropsychology and cognition*, *16*(6), 708–720.

Marsh, R. L., Hicks, J. L., & Cook, G. I. (2005). On the relationship between effort toward an ongoing task and cue detection in event-based prospective memory. *Journal of Experimental Psychology: Learning, Memory, and Cognition, 31*, 68–75.

Marsh, R. L., Hicks, J. L., & Cook, G. I. (2006). Task interference from prospective memories covaries with contextual associations of fulfilling them. *Memory & Cognition, 34,* 1037–1045.

Marsh, R. L., Hicks, J. L., & Hancock, T. W. (2000). On the interaction of ongoing cognitive activity and the nature of an event-based intention. *Applied Cognitive Psychology, 14,* S29–S41.

Marsh, R. L., Hicks, J. L., & Watson, V. (2002). The dynamics of intention retrieval and coordination of action in event-based prospective memory. *Journal of Experimental Psychology: Learning, Memory, and Cognition, 28*, 652–660.

Marsh, R. L., Hicks, J. L., Cook, G. I., Hansen, J. S., & Pallos, A. L. (2003). Interference to ongoing activities covaries with the characteristics of an event-based intention. *Journal of Experimental Psychology: Learning, Memory, and Cognition*, *298*, 861–870.

Marsh, R.L., & Hicks, J.L. (1998). Event-based prospective memory and executive control of working memory. *Journal of Experimental Psychology: Learning, Memory, and Cognition, 24*, 336–349.

Martin, M. (1986). Ageing and patterns of change in everyday memory and cognition. *Human Learning, 5,* 63-74.

Martin, M., & Schumann-Hengsteler, R. (2001). How task demands influence time-based prospective memory performance in young and older adults. *International Journal of Behavioral Development, 25,* 386–391.

Martin, M., Kliegel, M., & McDaniel, M. A. (2003). The involvement of executive functions in prospective memory performance of adults. *International Journal of Psychology, 38,* 195–206.

Masini A, Efrati C, Merli M, Nicolao F, Amodio P, Del Piccolo F, & Riggio, O. (2003). Effect of blood ammonia elevation following oral glutamine load on the psychometric performance of cirrhotic patients. *Metabolic Brain Disease*, *18*, 27–35.

Mattli, F., Zöllig, J., & West, R. (2011). Age-related differences in the temporal dynamics of prospective memory retrieval: A lifespan approach. *Neuropsychologia*, *49*(12), 3494–504.

May, C. P., Zacks, R. T., Hasher, L., & Multhaup, K. S. (1999). Inhibition in the processing of garden-path sentences. *Psychology and Aging, 14*, 304–313.

Maylor E A, Smith G, Della Sala S, & Logie R H. (2002). Prospective and retrospective memory in normal aging and dementia: An experimental study. *Memory and Cognition, 20*, 871–884.

Maylor, E. A. (1993). Aging and forgetting in prospective and retro- spective memory tasks. *Psychology & Aging, 3,* 420–428.

Maylor, E. A. (1995). Prospective memory in normal ageing and dementia. *Neurocase, 1,* 285–289.

Maylor, E. A. (1996). Age-related impairment in an event-based prospective memory task. *Psychology and Aging*, *11*, 74–79.

Maylor, E. A. (1998). Changes in event-based prospective memory across the adulthood. *Aging, Neuropsychology, and Cognition, 5,* 107–128.

Maylor, E. A., & Lavie, N. (1998). The influence of perceptual load on age differences in selective attention. *Psychology and Aging, 13,* 563–573.

Mayr, U. (2001). Age differences in the selection of mental sets: The role of inhibition, stimulus ambiguity, and response-set overlap. *Psychology and Aging, 16(1),* 96–109.

Mayr, U., & Keele, S. (2000). Changing internal constraints on action: The role of backward inhibition. J*ournal of Experimental Psychology: General, 129,* 4–26.

McCrea, M., Cordoba, J., Vessey, G., Blei, A.T., & Randolph, C. (1996). Neuropsychological characterization and detection of subclinical hepatic encephalopathy. *Archives of Neurology.* 53, 758–763.

McDaniel M, Einstein G, & Rendell P. (2008) The puzzle of inconsistent age- related declines in prospective memory: A multiprocess explanation. In K. Matthias, ed. *Prospective memory* (pp 141–160).

McDaniel, M. A, & Einstein, G. O. (2011). The neuropsychology of prospective memory in normal aging: A componential approach. *Neuropsychologia*. *49*(8), 2147–2155.

McDaniel, M. A., & Einstein, G. O. (2000). Strategic and automatic processes in prospective

memory retrieval: A multiprocess framework. *Applied Cognitive Psychology*, 14, S127–S144.

McDaniel, M. A., Einstein, G. O., Stout, A. C., & Morgan, Z. (2003). Aging and maintaining intentions over delays: Do it or lose it. *Psychology and Aging, 18*, 823–835.

McDaniel, M. A., Glisky, E. L., Rubin, S. R., Guynn, M. J., & Routhieaux, B. C. (1999). Prospective memory: A neuropsychological study. *Neuropsychology*, *13*, 103–110.

McDaniel, M. A., Guynn, M. J., Einstein, G. O., & Breneiser, J. (2004). Cue-focused and automatic-associative processes in prospective memory retrieval. *Journal of Experimental Psychology: Learning, Memory, and Cognition, 30,* 605–614.

McDaniel, M. A., Robinson-Riegler, B., & Einstein, G. O. (1998). Prospective remembering: Perceptually driven or conceptually driven processes? *Memory & Cognition, 26*, 121–134.

McFarland, C. P., & Glisky, E. L. (2009). Frontal lobe involvement in a task of time-based prospective memory. *Neuropsychologia*, *47*(7), 1660–1669.

McIntosh, A. R., Bookstein, F. L., Haxby, J.V., & Grady, C. L. (1996). Spatial pattern analysis of functional brain images using partial least squares. *NeuroImage,* 3, 143–157.

Mehndiratta, M.M., Sood, G.K., Sarin, S.K., & Gupta, M. (1990). Comparative evaluation of visual, somatosensory, and auditory evoked potentials in the detection of subclinical hepatic encephalopathy in patients with nonalcoholic cirrhosis. *American Journal of Gastroenterology*, *85*, 799–803.

Meiran, N. (2000). Modelling cognitive control in task-switching. *Psychological Research, 63,* 234–249

Melara, R. D., & Algom, D. (2003). Driven by information: a tectonic theory of Stroop effects. *Psychological Review, 110(3),* 422–471.

Menon, V., Adleman, N.E., White, C.D., Glover, G.H., & Reiss, A.L. (2001). Error-related brain activation during a Go/NoGo response inhibition task. *Human Brain Mapping*, *12*, 131–143.

Milham, M. P., Erickson, K. I., Banich, M. T., Kramer, A. F., Webb, A., Wszalek, T., et al. (2002).

Attentional control in the aging brain: Insights from an fMRI study of the Stroop task. *Brain and Cognition, 49(3),* 277–296.

Miniussi, C., Marzi, C. A., & Nobre, A. C. (2005). Modulation of brain activity by selective task sets observed using event-related potentials. *Neuropsychologia, 43,* 1514–1528.

Mitchell, J. P., Macrae, C. N., & Gilchrist, I. D. (2002). Working memory and the suppression of reflexive saccades. *Journal of Cognitive Neuroscience, 14(1),* 95–103.

Miyake, A., Friedman, N.P., Emerson, M.J., Witzki, A.H., & Howerter, A. (2000). The unity and diversity of executive functions and their contributions to complex ‘‘frontal lobe’’ tasks: A latent variable analysis. *Cognitive Psychology*, 41, 49–100.

Mondini, S., Mapelli, D., Vestri, A., Arcara, G., & Bisiacchi, P. S. (2011). Esame Neuropsicologico Breve 2. Milano, Italy: Raffaello cortina editore.

Monfort P, Muñoz MD, ElAyadi A, Kosenko E, & Felipo V. (2002) Effects of hyperammonemia and liver disease on glutamatergic neurotransmission. *Metabolic Brain Disease*, 17, 237–250.

Monsell, S. (1996). Control of mental processes. In V. Bruce (Ed.), *Unsolved mysteries of the mind: Tutorial essays in cognition* (pp. 93-148). Hove, England: Erlbaum, Taylor, & Francis.

Monsell, S. (2003). Task switching. *Trends in Cognitive Sciences, 7(3),* 134–140.

Montagnese, S., Amodio, P., & Morgan, M. Y. (2004). Methods for diagnosing hepatic encephalopathy in patients with cirrhosis: a multidimensional approach. *Metabolic brain disease*, *19(3-4),* 281-312.

Morris, N., & Jones, D. M. (1990). Memory updating in working memory: The role of the central executive. *British Journal of Psychology, 81,* 111–121.

Moscovitch, M. (1982). A neuropsychological approach to memory and perception in normal and pathological aging. In F. I. M. Craik & S. Trehub (Eds.), Aging and cognitive processes (pp. 55–78). New York: Plenum Press.

Moscovitch, M. (1994) Memory and working with memory: Evaluation of a component process

model and comparisons with other models. In: Schacter DL and Tulving E (eds.). *Memory Systems*, (pp. 269–310). Cambridge, MA: MIT Press.

Mouraux, A., & Iannetti, G.D. (2008). Across-trial averaging of event-related EEG responses and beyond. *Magnetic Resonance Imaging*, *26*, 1041–1054.

Muller, N.G., & Knight, R.T. (2002). Age-related changes in fronto-parietal networks during spatial memory: an ERP study. *Cognitive Brain Research*. *13*, 221–234.

Munka, L., & Berti, S. (2006). Examining task-dependencies of different attentional processes as reflected in the P3a and reorienting negativity components of the human event-related brain potential. *Neuroscience letters*, *396*(3).

Munoz, D.P., Broughton, J.R., Goldring, J.E., & Armstrong, I.T. (1998). Age-related performance of human subjects on saccadic eye movement tasks. *Experimental Brain Research, 121,* 391–400.

Murtha, S., Cismaru, R., Waechter, R., Chertkow, H. (2002). Increased variability accompanies frontal lobe damage in dementia. *Journal of International Neuropsychology Society*, *8*, 360–372.

Näätänen, R., Tervaniemi, M., Sussman, E., Paavilainen, P., & Winkler, I. (2001) "Primitive intelligence" in the auditory cortex. *Trends in Neuroscience*, *24*, 283–288.

Nieuwenhuis, S., Ridderinkhof, K. R., de Jong, R., Kok, A., & van der Molen, M. W. (2000). Inhibitory inefficiency and failures of intention activation: age-related decline in the control of saccadic eye movements. *Psychology and Aging, 15(4),* 635-647.

Nieuwenhuis, S., Yeung, N., van den Wildenberg, W., & Ridderinkhof, K. R. (2003). Electrophysiological correlates of anterior cingulate function in a go/no-go task: Effects of response conflict and trial type frequency. *Cognitive, Affective & Behavioral Neuroscience*, *3*, 17–26.

Nigg, J., (2000). On inhibition/disinhibition in developmental psychopathology: views from cognitive and personality psychology and a working inhibition taxonomy. *Psychological Bulletin, 126,* 220–246.

Nigg, J., (2001). Is ADHD a Disinhibitory Disorder? *Psychological Bulletin, 127,* 571– 598.

Norman, D.A., & Shallice, T. (1986). Attention to action: willed and automatic control of behaviour. In: Davidson, R.J., Schwartz, G.E., Shapiro, D. (Eds.), *Consciousness and Self-Regulation: Advances in Research and Theory.* (pp. 1–18). Plenum, New York.

Oberauer, K. (2002). Access to information in working memory: exploring the focus of attention. *Journal of Experimental Psychology: Learning, Memory and Cognition*, *28*, 411–421.

Oberauer, K. (2005). Binding and inhibition in working memory: Individual and age differences in short-term recognition. *Journal of Experimental Psychology: General, 134,* 368–387.

Oberauer, K., Suß, H.M., Schulze, R., Wilhelm, O. & Wittmann, W.W. (2000). Working memory capacity: Facets of a cognitive ability construct. *Personality and Individual Differences*, *29*, 1017–1045.

Oberauer, K., Wendland, M., & Kliegl, R. (2003). Age differences in working memory – the roles for storage and selective access. *Memory and Cognition, 31,* 563–569.

Okuda, J., Fujii, T., Ohtake, H., Tsukiura, T., Yamadori, A., Frith, C. D., et al. (2007). Differential involvement of regions of rostral prefrontal cortex (Brodmann area 10) in time- and event-based prospective memory. *International Journal of Psychophysiology*, *64(3)*, 233–246.

Oldfield, R.C. (1971) The assessment and analysis of handedness: the Edinburgh inventory. *Neuropsychologia, 9*, 97–113.

Onton, J., Westerfield, M., Townsend, J., & Makeig, S. (2006). Imaging human EEG dynamics using independent component analysis. *Neuroscience Biobehavioral Review, 30*, 808–822.

Owen, A. M., McMillan, K. M., Laird, A. R., & Bullmore, E. (2005). N-back working memory paradigm: a meta-analysis of normative functional neuroimaging studies. *Human brain mapping*, *25(1),* 46–59.

Pardo, J.V., Pardo, P.J., Janer, K.W., & Raichle, M.E., (1990). The anterior cingulate cortex mediates processing selection in the Stroop attentional conflict paradigm. *PNAS*, *87*, 256–259.

Park, D. C., & Gutchess, A. H. (2000). Cognitive aging and everyday life. *Cognitive Aging: A Primer,* 217–232.

Park, D. C., & Kidder, D. P. (1996). Prospective memory and medication adherence. In M. Brandimonte, G. O. Einstein, & M. A. McDaniel (Eds.), *Prospective memory: Theory and application* (pp. 369– 390). Mahwah, NJ: Erlbaum.

Park, D. C., & Reuter-Lorenz, P. (2009). The adaptive brain: aging and neurocognitive scaffolding. *Annual review of psychology*, *60*, 173-96.

Park, D. C., Hertzog, C., Kidder, D. P., Morrell, R. W., & Mayhorn, C. B. (1997). Effect of age on event-based and time-based prospective memory. *Psychology and Aging, 12,* 314–327.

Park, D. C., Smith, A. D., Lautenschlager, G., Earles, J. L., Frieske, D., Zwahr, M., & Gaines, C.L. (1996). Mediators of long-term memory performance across the life span. *Psychology and Aging, 11*(4), 621–637.

Park, D., & Reuter-Lorenz, P. A. (2009). The adaptive brain: Aging and neurocognitive scaffolding. *Annual Review of Psychology, 60,* 173–196.

Park, D.C., Lautenschlager, G., Hedden, T., Davidson, N.S., Smith, A.D., Smith, P.K. (2002). Models of visuospatial and verbal memory across the adult life span. *Psychology of Aging. 17(2),* 299–320.

Parsons-Smith, B.G., Summerskill, W.H.J., Dawson, A.M., & Sherlock, S. (1957). The electroencephalography in liver disease. *Lancet, 2*, 867–871.

Patton, G. W., & Meit, M. (1993). Effect of aging on prospective and incidental memory. *Experimental Aging Research, 19,* 165–176.

Paxton, J.L., Barch, D.M., Storandt, M., & Braver, T.S. (2006). Effects of environmental support and strategy training on older adults' use of context. *Psychology of Aging*, *21*, 499–509.

Perfect, T. J., & Maylor, E. A. (2000). Rejecting the dull hypothesis: The relation between method and theory in cognitive aging. In T. J. Perfect & E. A. Maylor (Eds.), *Models of cognitive*

aging (pp. 1–18). Oxford: Oxford University Press.

Persson, J., Lustig, C., Nelson, J. K., & Reuter-Lorenz, P. A. (2007). Age differences in deactivation: A link to cognitive control? *Journal of Cognitive Neuroscience, 19,* 1021–1032.

Pfefferbaum, A., & Ford, J. M. (1988). ERPs to stimuli requiring response production and inhibition: Effects of age, probability and visual noise. *Electroencephalography and Clinical Neurophysiology, 71,* 55–63.

Pfefferbaum, A., Ford, J.M., Weller, B. J., & Kopel, B. S. (1985). ERPs to response production and inhibition. *Electroencephalography and Clinical Neurophysiology, 60,* 423–434.

Picton, T.W., Stuss, D. T., Champagne, S. C., & Nelson, R. F. (1984). The effects of age on human event-related potentials. *Psychophysiology*, *21*, 312–325.

Pinheiro, J.C., & Bates, D.M. (2000). Mixed-Effects Models in S and S-PLUS. New York: Springer.

Polich, J. (1996). Meta-analysis of P300 normative aging studies. *Psychophysiology, 33,* 334–353.

Polich, J. (1997). On the relationship between EEG and P300: Individual differ- ences, aging, and ultradian rhythms. *International Journal of Psychophysiology*, *26*, 299–317.

Polich, J. (2003). Theoretical overview of P3a and P3b. In J. Polich (Ed.), *Detection of change: Event-related potential and fMRI findings* (pp. 83– 98). Boston: Kluwer Acadcemic Press.

Polich, J. (2007). Updating P300: An Integrative Theory of P3a and P3b. *North*, *118*(10), 2128–2148.

Pollack, I., Johnson, L.B., & Knaff, P.R. (1959). Running memory span. *Journal of Experimental Psychology*, *57*, 137–146.

Porjesz, B., & Begleiter, H. (1981). Human evoked brain potentials and alcohol. *Alcoholism*: *Clinical & Experimental Research, 5*, 304–317.

Posner, M.I. & Raichle, M.E. (1994). *Images of Mind.* Freeman: New York.

Posner, M.I., & Petersen, S.E. (1990). The attention system of the human brain. *Annual Review of Neuroscience, 13,* 25–42.

Proctor, R.W., Miles, J.D., & Baroni, G. (2011). Reaction time distribution analysis of spatial correspondence effects. *Psychonomic bulletin & review*, 242–266.

Rabbitt, P., Lowe, C., & Shilling, V. (2001). Frontal tests and models for cognitive ageing. *European Journal of Cognitive Psychology, 13*, 5–28.

Raichle, M. E., MacLeod, A. M., Snyder, A. Z., Powers, W. J., Gusnard, D. A., & Shulman, G. L. (2001). A default mode of brain function. Proceedings of the National Academy Sciences of the United States of America, *98*, 676–682.

Ramautar, J.R., Kok, A., & Ridderinkhof, K.R. (2004). Effects of stop-signal probability in the stop-signal paradigm: the N2/P3 complex further validated. *Brain and Cognition, 56(2),* 234–52.

Randall, W. M., & Smith, J. L. (2011). Conflict and inhibition in the cued-Go/NoGo task. *Clinical neurophysiology: official journal of the International Federation of Clinical Neurophysiology*, 3–10. International Federation of Clinical Neurophysiology.

Randolph, C., Hilsabeck, R., Kato, A., Kharbanda, P., Li, Y.-Y., Mapelli, D., Ravdin, L. D., Romero-Gomez, M., Stracciari, A. & Weissenborn, K. (2009), Neuropsychological assessment of hepatic encephalopathy: ISHEN practice guidelines. *Liver International, 29,* 629–635.

Ratcliff, R. (1979). Group reaction time distributions and an analysis of distribution statistics. *Psychological Bulletin*. 86, 446–461.

Raz, N. (2000). Aging of the brain and its impact on cognitive performance: Integration of structural and functional findings. In: F.I.M. Craik & T.A. Salthouse (Eds.), *Handbook of aging and cognition* (2nd ed., pp. 1–90). Mahwah, NJ: Erlbaum.

Regan, D. (1989). Human Brain Electrophysiology: Evoked Potentials and Evoked Magnetic Fields in Science and Medicine, Elsevier, New York, (pp. 167–482). Reitan, R.M.

Rendell, P. G., & Craik, F. I. M. (2000). Virtual week and actual week: Age-related differences in prospective memory. *Applied Cognitive Psychology, 14,* S43–S62.

Rendell, P. G., & Thomson, D. M. (1993). The effect of ageing on remembering to remember: An investigation of simulated medication regimens. *Australian Journal of Ageing, 12,* 11–18.

Rendell, P. G., Jensen, F., & Henry, J. D. (2007). Prospective memory in multiple sclerosis. *Journal of the International Neuropsychological Society, 13*, 410–416.

Rendell, P.G., McDaniel, M.A., Forbes, R.D., & Einstein, G.O. (2007). Age-related effects in prospective memory are modulated by ongoing task complexity and relation to target cue. *Neuropsychology, development, and cognition. Section B, Aging, neuropsychology and cognition*, *14*(3), 236-56.

Reuter-Lorenz, P. (2002). New visions of the aging mind and brain. *Trends in cognitive sciences*, *6(9),* 394.

Reuter-Lorenz, P. A., & Cappell, K. (2008). Neurocognitive aging and the compensation hypothesis. *Current Directions in Psychological Science, 18,* 177–182.

Reuter-Lorenz, P. A., & Park, D. C. (2010). Human Neuroscience and the Aging Mind : A New Look at Old Problems. *Science*, 405–415.

Reuter-Lorenz, P. A., & Sylvester, C.-Y. C. (2005). *The cognitive neuroscience of working memory and aging*. In R. Cabeza, L. Nyberg, & D. Park (Eds.), Cognitive neuroscience of aging: Linking cognitive and cerebral aging (pp. 186–217). Oxford: Oxford University Press.

Reuter-Lorenz, P. A., Jonides, J., Smith, E., Hartley, A., Miller, A., Marshuetz, C., & Koeppe, R. (2000). Age differences in the frontal lateralization of verbal and spatial working memory revealed by PET. *Journal of Cognitive Neuroscience, 12,* 174–187.

Reynolds, J. R., West, R., & Braver, T. (2009). Distinct Neural Circuits Support Transient and Sustained Processes in Prospective Memory and Working Memory, *Cerebral Cortex*, *19*, 1208–1221.

Ridderinkhof, K.R. (2002). Micro- and macro-adjustments of task set: activation and suppression in conflict tasks. *Psychological Research*, 66*,* 312–323.

Riis, J. L., Chong, H., Ryan, K. K., Wolk, D. A, Rentz, D. M., Holcomb, P. J., & Daffner, K. R. (2008). Compensatory neural activity distinguishes different patterns of normal cognitive aging. *NeuroImage*, *39*(1), 441–54.

Rikkers, L., Jenko, P., Rudman, D., & Freides, D. (1978). Subclinical hepatic encephalopathy: detection, prevalence, and relationship to nitrogen metabolism. *Gastroenterology, 75,* 462–469.

Roberts, L. E., Rau, H., Lutzenberger, W., & Birbaumer, N. (1994). Mapping P300 waves onto inhibition: Go/no-go discrimination. *Electroencephalography and Clinical Neurophysiology*, *92*, 44–55.

Roberts, R. J., Hager, L. D., & Heron, C. (1994). Prefrontal cognitive processes: Working memory and inhibition in the antisaccade task. *Journal of Experimental Psychology: General*, 123(4), 374–393.

Rogers, R. D., & Monsell, S. (1995). The cost of a predictable switch between simple cognitive tasks. *Journal of Experimental Psychology: General, 124*, 207–231.

Rohmer, F., & Kurtz, D. (1961). EEG et ammoniemie dans les troubles nerveux des affections. Atti del VII Congresso Internazionale di Neurologia. Roma, Edizioni per il Congresso, 115–163.

Romero, G.M., Cordoba, J., & Jover, R., (2006). Tablas de normalidad de la poblacion espanola para los tests psicometricos utilizados en el diagnostico de la encefalopatia hepatica minima. *Medicina Clinica (Barc), 127,* 246–249.

Rosen, A. C., Prull, M. W., O'Hara, R., Race, E. A., Desmond, J. E., Glover, G. H., et al. (2002). Variable effects of aging on frontal lobe contributions to memory. *Neuroreport*, *13*(18), 2425–2428.

Rosen, V. M., & Engle, R. W. (1998). Working memory capacity and suppression. *Journal of Memory & Language, 39*, 418-436.

Rosvold, H. E., Mirsky, A. F., Sarason, I., Bransome, E. D., & Beck, L. H. (1956). A continuous performance test of brain damage. *Journal of Consulting Psychology*, *20(5),* 343–350.

Roth, A., Roesch-Ely, D., Bender, S., Weisbrod, M., & Kaiser, S. (2007). Increased event-related potential latency and amplitude variability in schizophrenia detected through wavelet-based single trial analysis. *International Journal Psychophysiology*. 66, 244–254.

Rubia, K., Russell, T., Overmeyer, S., Brammer, M., Bullmore, E., Sharma, T., Simmons, A., Williams, S., Giampietro, V., Andrew, C., & Taylor, E. (2001). Mapping motor inhibition: conjunctive brain activa- tions across different versions of the go/no-go and stop tasks. *NeuroImage*, *13*, 250–261.

Rush, B.K., Barch, D.M., & Braver, T.S. (2006). Accounting for cognitive aging: context processing, inhibition or processing speed? *Neuropsychology, development, and cognition. Section B, Aging, neuropsychology and cognition*, *13*, 588–610.

Rushby, J.A., & Barry, R.J., 2009. Single-trial event-related potentials to significant stimuli. *International Journal of Psychophysiology, 74*, 120–131.

Rushworth, M. F., Passingham, R. E., & Nobre, A. C. (2002). Components of switching intentional set. *Journal of Cognitive Neuroscience, 14(8),* 1139–1150.

Rypma, B., & D'Esposito, M. (2001) Age-related changes in brain–behavior relationships: evidence from event-related functional MRI studies. *European Journal of Cognitive Psychology*. *13*, 235–256

Rypma, B., & D'Esposito, M. (1999). The roles of prefrontal brain regions in components of working memory: Effects of memory load and individual differences. *Proceedings of the National Academy of Sciences, U.S.A.,* 96, 6558–6563.

Rypma, B., & D'Esposito, M. (2000). Isolating the neural mechanisms of age-related changes in human working memory. *Nature Neuroscience*, *3*, 509–515.

Rypma, B., Eldreth, D. A., & Rebbechi, D. (2007). Age-related differences in activation-performance relations in delayed-response tasks: A multiple component analysis. *Cortex*, 43,

65–76.

Sabri, M., Liebenthal, E., Waldron, E.J., Medler, D.A., & Binder, J.R. (2006). Attentional modulation in the detection of irrelevant deviance: a simultaneous ERP/fMRI study. *Journal of Cognitive Neuroscience, 18,* 689–700.

Salthouse, T. A. (1996). The processing-speed theory of adult age differences in cognition. *Psychological Review, 103*, 403–428.

Salthouse, T. A., Atkinson, T. M., & Berish, D. E. (2003). Executive functioning as a poten- tial mediator of age-related cognitive decline in normal adults. *Journal of Experimental Psychology: General, 132,* 566–594.

Salthouse, T. A., Berish, D. E., & Siedlecki, K. L. (2004). Construct validity and age sensitivity of prospective memory. *Memory and Cognition*, *32(7),* 1133–1148.

Salthouse, T. A., Toth, J. P., Hancock, H. E., & Woodard, J. L. (1997). Controlled and automatic forms of memory and attention: Process purity and the uniqueness of age-related influences. *Journal of Gerontology: Psychological Sciences*, *52B*, P216–P228.

Sandford, N.L., & Saul, R.E. (1988). Assessment of hepatic encephalopathy with visual evoked potentials compared with conventional methods. *Hepatology*, *8*, 1094–1098.

Saville, C.W.N., Dean, R.O., Daley, D., Intriligator, J., Boehm, S., Feige, B., & Klein, C. (2011) Electrocortical correlates of intra-subject variability in reaction times: Average and single- trial analyses. *Biological Psychology*, *87*, 74–83.

Saxena, N., Bhatia, M., Joshi, Y.K., Garg, P.K., & Tandon, R.K. (2001). Auditory P300 event-related potentials and number connection test for evaluation of subclinical hepatic encephalopathy in patients with cirrhosis of the liver: A follow-up study. *Journal of Gastroenterology and Hepatology, 16,* 322–327.

Saxena, N., Bhatia, M., Joshi, Y.K., Garg, P.K., Dwivedi, S.N., & Tandon, R.K. (2002). Electrophysiological and neuropsychological tests for the diagnosis of subclinical hepatic encephalopathy and prediction of overt encephalopathy, *Liver, 22,*190–197.

Schiff, S., Mapelli, D., Vallesi, A., Orsato, R., Gatta, A., & Umilta, C. (2006). Top-down and bottom-up processes in the extrastriate cortex of cirrhotic patients : An ERP study. *Clinical Neurophysiology*, *117*, 1728–1736.

Schiff, S., Vallesi, A., Mapelli, D., Orsato, R., Pellegrini, A., Umiltà, C., Gatta, A., & Amodio, P., (2005). Impairment of response inhibition precedes motor alteration in the early stage of liver cirrhosis: a behavioral and electrophysiological study. *Metabolic Brain Disease, 20*, 381–392.

Schiff, S., Vallesi, A., Mapelli, D., Orsato, R., Pellegrini, A., Umiltà, C., Gatta, A., et al. (2005). Impairment of Response Inhibition Precedes Motor Alteration in the Early Stage of Liver Cirrhosis : A Behavioral and Electrophysiological Study. *Brain*, *20*(4), 381–392.

Schneider-Garces, N. J., Gordon, B. A., Brumback-Peltz, C. R., Shin, E., Lee, Y., Sutton, B. P., & Fabiani, M. (2010). Span, CRUNCH and beyond: Working memory capacity and the aging brain. *Journal of Cognitive Neuroscience*, *15*, 655–669.

Schneider, B. A., & Pichora-Fuller, M. K. (2000). Implications of perceptual deterioration for cognitive aging research. In F. I. M. Craik & T. A. Salthouse (Eds.), *Handbook of Cognitive Aging II* (pp. 155–219). Mahwah, NJ: Lawrence Erlbaum Associates, Inc.

Schomerus H, & Hamster W. (1998). Neuropsychological aspects of portal-systemic encephalopathy. *Metabolic Brain Disease*, 13, 361–377.

Schomerus, H., & Schreiegg, J. (1993). Prevalence of latent portasystemic encephalopathy in an unselected population of patients with liver cirrhosis in general practice. *Zeitschrift fur Gastroenterologie, 31,* 231–234.

Schomerus, H., Hamster, W., Blunck, H., Reinhard, U., Mayer, K., & Dolle, W. (1981). Latent portasystemic encephalopathy. I. Nature of cerebral functional defects and their effect on fitness to drive. *Digestive Diseases and Sciences, 26,* 622–630.

Schröger, E., & Wolff, C., (1997). Fast preattentive processing of location: a functional basis for selective listening in humans. *Neuroscience Letters*, *232*, 5–8.

Schröger, E., & Wolff, C., (1998a). Attentional orienting and reorienting is indicated by human event-related brain potentials. *NeuroReport, 9*, 3355–3358.

Schröger, E., & Wolff, C., (1998b). Behavioral and electrophysiological effects of task-irrelevant sound change: a new distraction paradigm. *Brain Research. Cognitive Brain Research*. *7*, 71–87.

Scullin, M. K., Mcdaniel, M. A., & Einstein, G. O. (2010). Control of Cost in Prospective Memory : Evidence for Spontaneous Retrieval Processes. *Cognition*, *36*(1), 190 -203.

Shallice, T. (1982). Specific impairments of planning. Philosophical Transactions, Royal Society of London. B. *Biological Science*, *298*, 199–209.

Shallice, T., (1988). From Neuropsychology to Mental Structure. Cambridge University Press, New York.

Shallice, T., & Burgess, P. W. (1991). Deficits in strategy application following frontal lobe damage in man. *Brain*, 114, 727–741.

Shawcross, D., & Jalan, R. (2005). The pathophysiologic basis of hepatic encephalopathy: central role for ammonia and inflammation. *Cellular* and *Molecular Life Sciences*, *62*, 2295–2304.

Sherlock, S. Summerskill, W.H., White, L.P., & Phear, E.A. (1954). Portal-systemic encephalopathy; neurological complications of liver disease. *Lancet, 267,* 454–457.

Sherlock, S., & Dooley, J. (2002). Hepatic encephalopathy. In: *Diseases of the Liver and Biliary System*. 11th ed. Oxford: Blackwell Publishing, (pp. 93-109).

Simon, J. R., & Rudell, A. P. (1967). Auditory S–R compatibility: The effect of an irrelevant cue on information processing. *Journal of Applied Psychology, 51,* 300–304.

Simon, J.R., 2011. "The Simon effect": A potent behavioral mechanism. *Acta Psychologica*, 136–181

Simson, R.C., Vaughan, H.G., & Ritter,W. (1977). The scalp topography of potentials in auditory and visual Go/NoGo tasks. *Electroencephalography and Clinical Neurophysiology, 43,* 864–875.

Smith, R. E. (2003). The cost of remembering to remember in event-based prospective memory: Investigating the capacity demands of delayed intention performance. *Journal of Experimental Psychology: Learning, Memory, and Cognition*, *29*, 347–361.

Smith, R. E. (2010). What Costs Do Reveal and Moving Beyond the Cost Debate: Reply to Einstein and McDaniel. *Journal of experimental psychology. Learning, memory, and cognition*, *36*(4), 1089–1095.

Smith, R. E., & Bayen, U. J. (2004). A multinomial model of event-based prospective memory. *Journal of experimental psychology. Learning, memory, and cognition*, *30(4),* 756–77.

Smith, R. E., Hunt, R. R., McVay, J. C., & McConnell, M. D. (2007). The cost of event-based prospective memory: salient target events. *Journal of experimental psychology. Learning, memory, and cognition*, *33(4),* 734–46.

Snyder, E., & Hillyard, S.A. (1976). Long-latency evoked potentials to irrelevant, deviant stimuli. *Behavioral Biology*, *16*, 319–331.

Sorensen, M., & Keiding, S. (2007). New findings on cerebral ammonia uptake in HE using functional 13N-ammonia PET. *Metabolic Brain Disease, 22*, 277–284.

Sotil, E.U., Gottstein, J,, Ayala, E., Randolph, C., & Blei, A.T. (2009). Impact of preoperative overt hepatic encephalopathy on neurocognitive function after liver transplantation. *Liver Transplantation journal, 15,* 184–192.

Sparacino, G., Milani, S., Arslan, E., & Cobelli, C. (2002). A Bayesian approach to estimate evoked potentials. *Computer Methods and Programs in Biomedicine, 68,* 233–248.

Spieler, D.H., Balota, D.A., & Faust, M.E. (1996). Stroop performance in healthy younger and older adults and in individuals with dementia of the Alhzheimer´s type. *Journal of Experimental Psychology, 22,* 461–479.

Stern Y. 2(002). What is cognitive reserve? Theory and research application of the reserve concept. *Journal of International Neuropsychology Society*, *8(3),* 448–60

Stern, Y. (2009). Cognitive reserve. *Neuropscyhologia*, *47*, 2015–2028.

Stroop, J.R. (1935). Studies of interference in serial verbal reactions. *Journal of Experimental Psycholology, 18,* 643–662.

Stuss D.T., Pogue J., Buckle, L., & Bondar, J. (1994). Characterization of stability of performance in patients with traumatic brain injury: variability and consistency on reaction time tests. *Neuropsychology*, 316–324.

Stuss, D.T., Floden, D., Alexander, M.P., Levine, B., & Katz, D. (2001). Stroop performance in focal lesion patients: Dissociation of processes and frontal lobe lesion location *Neuropsychologia, 39*, 771–786.

Stuss, D.T., Murphy, K.J., Binns, M.A., & Alexander, M.P. (2003). Staying on the job: the frontal lobes control individual performance variability. *Brain*, *126*, 2363–2380.

Sylvester, C.Y., Wager, T.D., Lacey, S.C., Hernandez, L., Nichols, T.E., Smith, E.E., & Jonides, J. (2003). Switching attention and resolving interference: fMRI measures of executive functions. *Neuropsychologia*, *41*, 357– 370.

Tarantino, V., Cona, G., Bianchin, M., & Bisiacchi, S.P. (submitted). Monitoring mechanisms in time- and event-based prospective memory. *Memory.*

Tarter, R.E., Hegedus, A.M., Van Thiel, D.H., Schade, R.R., Gavaler, J.S., & Starzl, T.E. (1984). Non-alcoholic cirrhosis associated with neuropsychological dysfunction in the absence of overt evidence of hepatic encephalopathy. *Gastroenterology, 86,* 1421–1427.

Tarter, R.E., Panzak, G., Switala, J., Lu, S., Simkevitz, H., & Van Thiel, D. (1997). Isokinetic muscle strength and its association with neuropsychological capacity in cirrhotic alcoholics. *Alcoholism*: *Clinical & Experimental Research, 21,* 191–196.

Themanson, J. R., Hillman, C. H., & Curtin, J. J. (2006). Age and physical activity influences on action monitoring during task switching. *Neurobiology of Aging, 27,* 1335–1345.

Titov, N., & Knight, R. G. (1997). Adult age differences in controlled and automatic memory processing. *Psychology and Aging*, *12*, 565–573.

Tolan, G. A., & Tehan, G. (1999). Determinants of short-term forgetting: Decay, retroactive interference, or proactive interference? *International Journal of Psychology, 34,* 285–292.

Travers, S., & West, R. (2008). Neural correlates of cue retrieval, task set configuration, and rule mapping in the explicit cue task switching paradigm. *Psychophysiology, 45,* 588–601.

Troyer, A. K., & Murphy, K. J. (2007). Memory for intentions in amnestic mild cog- nitive impairment: Time- and event-based prospective memory. *Journal of the International Neuropsychological Society*, *13*, 365–369.

Uttl, B. (2008). Transparent meta-analysis of prospective memory and aging. *PloS one*, *3*(2), e1568.

Uttl, B. (2011). Transparent Meta-Analysis: Does Aging Spare Prospective Memory with Focal vs. Non-Focal Cues? *PloS one*, *6*(2), e16618.

Uttl, B., & Graf, P. (1997). Color-Word Stroop test performance across the adult life span. *Journal of Clinical and Experimental Neuropsychology, 19(3),* 405–420.

Valle-Inclán, F. (1996). The locus of interference in the Simon effect: An ERP study. *Biological Psychology, 43*,147–162.

Vallesi, A. (2011). Targets and non- targets in the aging brain: a go/nogo Event-related Potential study. *Neuroscience Letters, 487 (3),* 313–317.

Vallesi, A., & Stuss, D. T. (2010). Excessive sub-threshold motor preparation for non-target stimuli in normal aging. *NeuroImage*, *50*(3), 1251-7.

Vallesi, A., Mapelli, D., Schiff, S., Amodio, P., & Umiltà, C. (2005). Horizontal and vertical Simon effect: different underlying mechanisms? *Cognition*, *96*, B33-B43.

Vallesi, A., Stuss, D. T., McIntosh, A. R., & Picton, T. W. (2009). Age-related differences in processing irrelevant information: evidence from event-related potentials. *Neuropsychologia*, *47*(2), 577-86.

Van Asselen, M., & Ridderinkhof, K. R. (2000). Shift costs of predictable and unexpected set

shifting in young and older adults. *Psychologica Beligica, 40,* 259–273.

Van Boxtel, G. J., van der Molen, M.W., Jennings, J. R., & Brunia, C. H. (2001).A psychophysiological analysis of inhibitory motor control in the stop-signal paradigm. *Biological Psychology, 58,* 229–262.

Van Boxtel, M. P., Ten Tusscher, M. P., Metsemakers, J. F., Willems, B., & Jolles, J. (2001). Visual determinants of reduced performance on the Stroop color-word test in normal aging individuals. *Journal of Clinical Experimental Neuropsychology, 23(5),* 620–627.

Van der Linden, M., Bredart, S., & Beerten, A. (1994). Age-related differences in updating working memory. *British Journal of Psychology, 85,* 145–152.

Van der Rijt, C.C., & Schalm, S.W. (1992). Quantitative EEG analysis and evoked potentials to measure (latent) hepatic encephalopathy. *Journal of Hepatology, 14,* 141–142.

Van der Rijt, C.C., Schalm, S.W., De Groot, G. H., & De Vlieger, M. (1984). Objective measurement of hepatic encephalopathy by means of automated EEG analysis. *Electroencephalography and Clinical Neurophysiology, 57,* 423–426.

Vaughan, L., Basak, C., Hartman, M., & Verhaeghen, P. (2008). Aging and working memory inside and outside the focus of attention: Dissociations of availability and accessibility. *Aging, Neuropsychology, and Cognition, 15(3),* 1–22.

Verhaeghen, P. (2011). Aging and Executive Control: Reports of a Demise Greatly Exaggerated. *Current Directions in Psychological Science*, *20*(3), 174–180.

Verhaeghen, P., & Basak, C. (2005). Ageing and switching of the focus of attention in working memory: results from a modified N -Back task. *The Quarterly Journal of Experimental Psychology: Section A*, *58*(1), 134–154.

Verhaeghen, P., & De Meersman, L. (1998). Aging and the Stroop effect: A meta-analysis. *Psychology and Aging, 13,* 120–126.

Verhaeghen, P., & Hoyer, W. J. (2007). Aging, focus switching, and task switching in a continuous calculation task: evidence toward a new working memory control process.

Neuropsychology, development, and cognition. Section B, Aging, neuropsychology and cognition, *14*(1), 22–39.

Verhaeghen, P., Cerella, J., Bopp, K. L., & Basak, C. (2005). Aging and varieties of cognitive control: A review of meta-analyses on resistance to interference, coordination and task switching, and an experimental exploration of age-sensitivity in the newly identified process of focus switching. In R. W. Engle, G. Sedek, U. Von Hecker, & D. N. McIntosh (Eds), *Cognitive limits in aging and psychopathology: Attention, working memory, and executive functions* (pp. 160–189). New York: Cambridge University Press.

Verleger, R. (1997). On the utility of P3 latency as an index of mental chronometry. *Psychophysiology, 34,*131–56.

Verleger, R., Jaskowski, P., & Wascher, E. (2005). Evidence for an Integrative role of P3b in linking reaction times to perception. *Journal of Psychophysiology, 19,* 165–181.

Virtaniemi, J., Kuusisto, J., Karjalainen, L., Karjalainen, S., & Laakso, M. (1995). Improvement of metabolic control does not normalize auditory brainstem latencies in subjects with insulin-dependent diabetes mellitus. *American Journal of Otolaryngology*, *16*, 172–176.

Volle, E., Gonen-Yaacovi, G., Costello, A. D. L., Gilbert, S. J., & Burgess, P. W. (2011). The role of rostral prefrontal cortex in prospective memory: A voxel-based lesion study. *Neuropsychologia*. *49(8*), 2185–2198.

Walhovd, K.B., Rosquist, H., & Fjell, A.M. (2008). P300 amplitude age reductions are not caused by latency jitter. *Psychophysiology*, *45*, 545–553.

Weissenborn K & Kolbe H. (1998). The basal ganglia and portal– systemic encephalopathy. *Metabolic Brain Disease, 13,* 261– 272.

Weissenborn K, Rückert, N., Brassel, F., Becker, H., & Dietz, H. (1996). A proposed modification of the Wada test for pre-surgical assessment in temporal lobe epilepsy. *Neuroradiology, 38,* 422–429.

Weissenborn, K. (1998). Diagnosis of encephalopathy. *Digestion 59(Suppl. 2)*, 22–24.

Weissenborn, K., Bokemeyer, M., Krause, J., Ennen, J., & Ahl, B. (2005). Neurological and neuropsychiatric syndromes associated with liver disease. *AIDS* (London, England), *19 Suppl 3*, S93–8.

Weissenborn, K., Ennen, J. C., Schomerus, H., Rückert, N., & Hecker, H. (2001a). Neuropsychological characterization of hepatic encephalopathy. *Journal of Hepatology, 34(5),* 768–73.

Weissenborn, K., Heidenreich, S., Ennen, J., Rückert, N., & Hecker, H. (2001b). Attention deficits in minimal hepatic encephalopathy. *Metabolic brain disease, 16(1-2),* 13–9.

Weissenborn, K., Heidenreich, S., Giewekemeyer, K., Rückert & Hecker, H. (2003). Memory function in early hepatic encephalopathy. *Journal of Hepatology. 39(3),* 320–325.

Weissenborn, K., Scholz, M., Hinrichs, H., Wiltfang, J., Schmidt, F.W., & Kunkel, H. (1990). Neurophysiological assessment of early hepatic encephalopathy. *Electroencephalography and Clinical Neurophysiology, 75,* 289–295.

West, R. (2004). The effects of aging on controlled attention and conflict processing in the Stroop task. *Journal of Cognitive Neuroscience, 16,* 103–113.

West, R. (2011). The temporal dynamics of prospective memory: A review of the ERP and prospective memory literature. *Neuropsychologia, 49,* 2233–2245.

West, R. L. (1996). An application of prefrontal cortex function theory to cognitive aging. *Psychological Bulletin*, *120*, 272–292.

West, R. L. (2007). The influence of strategic monitoring on the neural correlates of prospective memory. *Memory & Cognition, 35(5),* 1034–1046.

West, R. L., & Ross-Munroe, K. (2002). Neural correlates of the formation and realiza- tion of delayed intentions. *Cognitive, Affective, & Behavioral Neuroscience, 2(2),* 162–173.

West, R. L., & Wymbs, N. (2004). Is detecting prospective cues the same as selecting targets? An ERP study. *Cognitive, Affective, & Behavioral Neuroscience, 4(3),* 354–363.

West, R. L., Herndon, R. W., & Crewdson, S. J. (2001). Neural activity associated with the realization of a delayed intention. *Cognitive Brain Research, 12(1),* 1–9.

West, R. L., Wymbs, N., Jakubek, K., & Herndon, R. W. (2003). Effects of intention load and background context on prospective remembering: An event-related brain potential study. *Psychophysiology, 40(2),* 260–276.

West, R., & Alain, C. (2000). Effects of task context and fluctuations of attention on the neural activity supporting performance of the Stroop task. *Brain Research, 873,* 102–111.

West, R., & Bowry, R. (2005). Effects of aging and working memory demands on prospective memory. *Psychophysiology*, *42*(6), 698–712.

West, R., & Covell, E. (2001) Effects of aging on event-related neural activity related to prospective remembering. *Neuroreport*, *12*, 2855–2858.

West, R., & Craik, F. I. M. (2001). Influences on the efficiency of prospective memory in younger and older adults. *Psychology and Aging*, *16*, 682–696.

West, R., & Krompinger, J. (2005). Neural correlates of prospective and retrospective memory. *Neuropsychologia*, *43,* 418–433.

West, R., & Moore, K. (2005). Adjustments of cognitive control in younger and older adults. *Cortex, 41(4),* 570–581.

West, R., & Schwarb, H. (2006). The influence of aging and frontal function on the neural correlates of regulative and evaluative aspects of cognitive control. *Neuropsychology*, *20(4),* 468–481.

West, R., Herndon, R. W., & Covell, E. (2003). Neural Correlates of Age-Related Declines in the Formation and Realization of Delayed Intentions. *Psychology and Aging*, *18*(3), 461–473.

West, R., Jakubek, K., Wymbs, N., Perry, M., & Moore, K. (2005). Neural correlates of conflict processing. *Experimental Brain Research, 167,* 38–48

West, R., McNerney, M.W., Travers, S. (2007). Gone but not forgotten: the effects of cancelled

intentions on the neural correlates of prospective memory. *International Journal of Psychophysiology*, *64*, 215–225.

West, R., Scolaro, A. J., & Bailey, K. (2011). When goals collide: the interaction between prospective memory and task switching. *Canadian journal of experimental psychology = Revue canadienne de psychologie expérimentale*, *65*(1), 38–47.

West, R.L. (1999). Age differences in lapses of intention in the Stroop task. *Journal of Gerontology: Psychological Sciences, 54B,* P34–P43.

Wild-Wall, N., Willemssen, R., Falkenstein, M., & Beste, C. (2008). Time estimation in healthy ageing and neurodegenerative basal ganglia disorders. *Neuroscience Letters, 442(1),* 34–38.

Williams, B.R., Hultsch, D.F., Strauss, E.H., Hunter, M.A., & Tannock, R. (2005). Inconsistency in reaction time across the life span. *Neuropsychology*, *19*, 88–96.

Williams, B.R., Ponesse, J.S., Schachar, R., Logan, G.D., & Tannock, R. (1999). Development of inhibitory control across the lifespan. *Developmental Psychology, 35,* 205–213.

Wilson, S. P., & Kipp, K. (1998). The development of efficient inhibition: Evidence from directed-forgetting tasks. *Developmental Review, 18*, 86–123.

Winocur, G., & Moscovitch, M. (1983). Paired-associate learning in institutionalized and non institutionalized old people: An analysis of interference and context effects. *Journal of Gerontology, 38,* 455–464.

Yang, S.S., Chu, N., & Wu, C. (1997). The role of somatosensory evoked potentials on hepatic encephalopathy. *Biomedical Engineering*: *Applications*, *Basis* and *Communications,* 9, 154–157.

Zacks, R. T., & Hasher, L. (1994). Directed ignoring: Inhibitory regulation of working memory. In D. Dagenback & T. H. Carr (Eds.), *Inhibitory mechanisms in attention, memory and language* (pp. 241–264). New York, NY: Academic Press.

Zacks, R. T., Hasher, L., & Li, K. Z. H. (2000). Human memory. In F. I. M. Craik & T. A. Salthouse (Eds.), *The handbook of aging and cognition* (2nd ed.). Mahwah, NJ: Lawrence

Erlbaum Associates, Inc.

Zeef, E.J., Sonke, C.J., Kok, A., Buiten, M.M., & Kenemans, J.L. (1996). Perceptual factors affecting age-related differences in focused attention: performance and psychophysical analyses. *Psychophysiology, 33(5),* 555–565.

Zeegen, R., Drinkwater, J.E., & Dawson, A.M. (1970). Method for measuring cerebral dysfunction in patients with liver disease. *British Medical Journal*, *2*, 633–636.

Zeintl, M., Kliegel, M., & Hofer, S. M. (2007). The Role of Processing Resources in Age-Related Prospective and Retrospective Memory Within Old Age. *Psychology and Aging*, *22*(4), 826–834.

Zeintl, M., Kliegel, M., Rast, P., & Zimprich, D. (2006). Prospective memory complaints can be predicted by prospective memory performance in older adults. *Dementia and Geriatric Cognitive Disorders, 22,* 209–215.

Zhang, L.J., Yang, G., Yin, J., Liu, Y., & Qi, J. (2007). Abnormal default-mode network activation in cirrhotic patients: a functional magnetic resonance imaging study. *Acta Radiologica*, *48*, 781–787.

Zimmerman, T. D., & Meier, B. (2006). The rise and decline of prospective memory performance across the lifespan. *The Quarterly Journal of Experimental Psychology, 59,* 2040-2046.

Zimmermann, P., & Fimm, B. (1989*). Neuropsychologische Testbatterie zur Erfassung von Aufmerk samkeitsdefiziten*—Revidierte Fassung, Psychologisches Institut der Universitat Freiburg, Freiburg.

Zöllig, J., West, R. L., Martin, M., Altgassen, M., Lemke, U., & Kliegel, M. (2007). Neural correlates of prospective memory across the lifespan. *Neuropsychologia, 45(14),* 3299–3314.